To. Jan

Access DB# 106394 (4)

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Brian Kwon Examiner #: 78155 Date: 10/21/03
Art Unit: 1614 Phone Number 30 8-5377 Serial Number: 10/088958
Mail Box and Bldg/Room Location: CM1 1004 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Use of aryl piperidine carbamate NK1 + Gaba analog

Inventors (please provide full names): Hughes et al.

Earliest Priority Filing Date: 10/1998

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

- NK1 receptor antagonist + Gaba analog

specifically - [2-(1H-indol-3yl)-1-methyl-1-(1-phenyl-ethyl-carbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [2R-1R*,3S*]] as NK1 receptor antagonist

- gabapentin + pregabalin as GABA analogs

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 - 703-308-4498
jan.delaval@uspto.gov

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: Jan	NA Sequence (#)		STN	✓
Searcher Phone #: 4498	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)	✓	Questel/Orbit	
Date Searcher Picked Up: 10/28/03	Bibliographic		Dr.Link	
Date Completed: 10/28/03	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	Fulltext		Sequence Systems	
Clerical Prep Time: 15	Patent Family		WWW/Internet	
Online Time: + 50	Other		Other (specify)	

PTO-1590 (8-01)

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     (FILE 'HOME' ENTERED AT 11:35:18 ON 28 OCT 2003)

     FILE 'CAPLUS' ENTERED AT 11:35:27 ON 28 OCT 2003
                E HUGHES J/AU
L1         1027 S E3-49
                E HUGHES JOHN/AU
L2          576 S E3-57
L3         1602 S L1-2
                E SINGH L/AU
L4          395 S E3-25
                E E
                E SINGH L/AU
L5           56 S E36
L6            8 S E39
L7          459 S L4-6
                E WO2000-EP10084/AP,PRN
L8            1 S E3-4
                SEL RN

     FILE 'REGISTRY' ENTERED AT 11:45:11 ON 28 OCT 2003
L9            4 S E1-4
L10           1 S L9 AND C30H29N3O4
                E C30H29N3O4/MF
L11         213 S E3
L12         103 S L11 AND 5/NR
L13        2221 S (OC4-C6 AND NC4-C6 AND C6)/ES
L14           5 S L13 AND L12
L15           3 S L14 NOT (14C OR TRITIUM)
L16           3 S L10 OR L15
                SEL RN
L17           0 S E1-E3/CRN

     FILE 'CAPLUS' ENTERED AT 12:02:12 ON 28 OCT 2003
L18          18 S L16
L19          14 S CI 1021 OR CI1021 OR PD154075 OR PD()(154075 OR 154 075)
L20          20 S L18 OR L19
L21          10 S L20 AND (PY<=1999 OR PRY<=1999 OR AY<=1999)
L22           6 S L1-L7 AND L20
L23          12 S L21-22

     FILE 'USPATFULL' ENTERED AT 12:07:51 ON 28 OCT 2003
L24           9 S L20

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FILE 'REGISTRY' ENTERED AT 12:13:01 ON 28 OCT 2003
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   27 OCT 2003  HIGHEST RN 609766-09-8
DICTIONARY FILE UPDATES:  27 OCT 2003  HIGHEST RN 609766-09-8

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

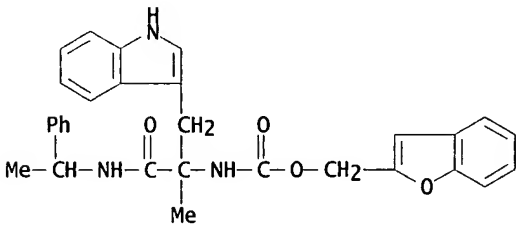
Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
```

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 - 703-308-4498
jan.delaval@uspto.gov

http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can l16 tot

L16 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 377076-61-4 REGISTRY
CN Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C30 H29 N3 O4**
SR CA
LC STN Files: CA, CAPLUS



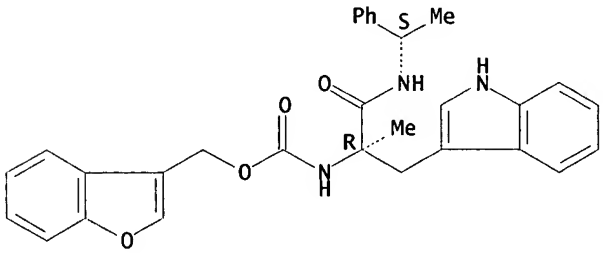
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:11205

L16 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 169475-89-2 REGISTRY
CN Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 3-benzofuranylmethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C30 H29 N3 O4**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

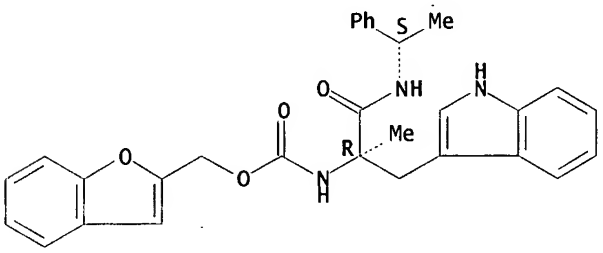
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 126:171893

REFERENCE 2: 123:275215

L16 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN **158991-23-2** REGISTRY
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 2-benzofuranylmethyl ester, [R-(R*,S*)]-
OTHER NAMES:
CN CI 1021
CN PD 154075
FS STEREOSEARCH
MF **C30 H29 N3 O4**
SR CA
LC STN Files: ADISINSIGHT, BIOBUSINESS, BIOSIS, CA, CAPLUS, CIN, DRUGNL, DRUGUPDATES, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16 REFERENCES IN FILE CA (1907 TO DATE)
16 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:160766

REFERENCE 2: 137:337901

REFERENCE 3: 137:329330

REFERENCE 4: 136:31709

REFERENCE 5: 135:162091

REFERENCE 6: 135:117245

REFERENCE 7: 134:285590

REFERENCE 8: 134:141620

REFERENCE 9: 133:120391

REFERENCE 10: 131:299365

=> b cap
FILE 'CAPLUS' ENTERED AT 12:13:54 ON 28 OCT 2003
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FILE COVERS 1907 - 28 Oct 2003 VOL 139 ISS 18
FILE LAST UPDATED: 27 Oct 2003 (20031027/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

=> d all hitstr tot l23

L23 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:417501 CAPLUS
DN 135:162091
TI Utilization of an Intramolecular Hydrogen Bond To Increase the CNS Penetration of an NK1 Receptor Antagonist
AU Ashwood, Valerie A.; Field, Mark J.; Horwell, David C.; Julien-Larose, Christine; Lewthwaite, Russell A.; McCleary, Scott; Pritchard, Martyn C.; Raphy, Jenny; **Singh, Lakhbir**
CS Pfizer Global Research and Development Cambridge University Forvie Site, Cambridge, CB2 2QB, UK
SO Journal of Medicinal Chemistry (2001), 44(14), 2276-2285
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 28
OS CASREACT 135:162091
AB This paper describes the synthesis and phys. and biol. effects of introducing different substituents at the .alpha.-position of the tryptophan contg. neurokinin-1 receptor antagonist [(R)-2-(1H-indol-3-yl)-1-methyl-1-((S)-1-phenyl-ethylcarbamoyl)ethyl]carbamic acid benzofuran-2-yl-Me ester (CI 1021). The described compds. all exhibit less than 5 nM binding affinities for the human neurokinin-1 receptor and selectivity over the tachykinin NK2 and NK3 receptor subtypes. Application of variable temp. NMR spectroscopy studies of the amide and urethane protons was utilized to det. the existence of an intramol. hydrogen bond. This intramol. hydrogen bond increases the apparent lipophilicity to allow increased central nervous system penetration and pharmacol. activity (gerbil foot tap test) in the case of the highest affinity compd. [(S)-1-dimethylaminomethyl-2-(1H-indol-3-yl)-1-((S)-1-phenyl-ethylcarbamoyl)ethyl]carbamic acid benzofuran-2-yl-Me ester (PD 174424) over those analogs that could not form an intramol. hydrogen bond.
ST structure activity NK1 receptor antagonist prepn hydrogen bond; mol modeling tachykinin receptor antagonist structure activity prepn
IT Tachykinin receptors
(NK1 antagonists; synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
IT Tachykinin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NK2; synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
IT Tachykinin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NK3; synthesis and structure activity relationships of a series of NK1

receptor antagonists with increased CNS penetration)
IT Biological transport
(drug; synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
IT Hydrogen bond
(intramol.; synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
IT Conformation
Lipophilicity
Molecular modeling
Structure-activity relationship
(synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
IT 32315-10-9, Triphosgene
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of)
IT 232953-47-8P 232953-51-4P 354117-37-6P 354117-38-7P 354117-39-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
IT 158991-23-2, CI 1021 354117-20-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
IT 75-03-6, Iodoethane 107-18-6, Allyl alcohol, reactions 501-53-1, Benzyl chloroformate 2279-15-4 2627-86-3, (S)-Methylbenzylamine 3756-30-7 13057-19-7 30438-74-5 55038-01-2, 2-Benzofuranylmethanol 354117-40-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
IT 346440-85-5P 346440-91-3P 346440-93-5P 346440-95-7P 346440-97-9P 346441-00-7P 346441-01-8P 346441-02-9P 346441-03-0P 354117-18-3P 354117-19-4P 354117-21-8P 354117-22-9P 354117-23-0P 354117-24-1P 354117-25-2P 354117-26-3P 354117-27-4P 354117-28-5P 354117-29-6P 354117-30-9P 354117-31-0P 354117-32-1P 354117-33-2P 354117-34-3P 354117-35-4P 354117-36-5P 354117-41-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anantharamaiah, G; Tetrahedron Lett 1982, V23, P3335 CAPLUS
(2) Bourne, G; J Chem Soc, Perkin Trans 1 1991, V7, P1693
(3) Boyle, S; Bioorg Med Chem 1994, V2, P357 CAPLUS
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(12) Guard, S; Neurochem Int 1991, V18, P149 CAPLUS
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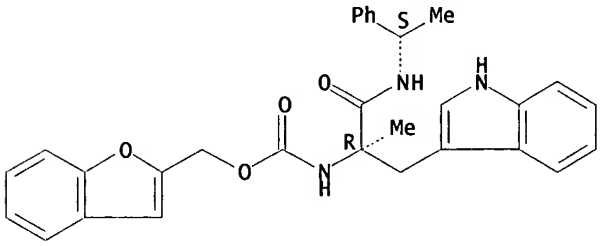
(16) Lide, D; Handbook of Chemistry and Physics, 73rd ed 1992, P3
(17) Lipinski, C; Adv Drug Delivery Rev 1997, V23, P3 CAPLUS
(18) Maggi, C; J Auton Pharmacol 1993, V13, P23 CAPLUS
(19) March, J; Advanced Organic Chemistry, 3rd ed 1995, P72
(20) Schollkopf, U; Liebigs Ann Chem 1985, P413

(21) Seward, E; Expert Opin Ther Pat 1999, V9, P571 CAPLUS
(22) Singh, L; Eur J Pharmacol 1997, V321, P209 CAPLUS
(23) Swain, C; Annu Rep Med Chem 1999, V34, P51 CAPLUS
(24) Tripos Associates; Sybil 6.6
(25) Turk, J; J Org Chem 1975, V40, P953 CAPLUS
(26) Yee, C; J Org Chem 1992, V57, P3525 CAPLUS
(27) Zhang, L; J Org Chem 1995, V60, P5719 CAPLUS
IT **158991-23-2, CI 1021**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and structure activity relationships of a series of NK1 receptor antagonists with increased CNS penetration)
RN 158991-23-2 CAPLUS
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L23 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:265246 CAPLUS
DN 134:285590
TI Pharmaceutical compositions comprising synergistic combinations of a NK1 receptor antagonist and a GABA analog for the treatment of psychiatric disorders
IN **Hughes, John; Singh, Lakhbir**
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-195
ICS A61K031-404; A61K031-40; A61P025-18; A61P025-24; A61K045-06; A61K031-40; A61K031-195
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001024791	A1	20010412	WO 2000-EP10084	20001009 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1233766	A1	20020828	EP 2000-979495	20001009 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003510355	T2	20030318	JP 2001-527790	20001009 <--

PRAI US 1999-158271P P 19991007 <--
WO 2000-EP10084 W 20001009

AB The present invention provides methods of treatment using synergistic combinations of an NK1 receptor antagonist and a GABA analog, and pharmaceutical compns. and products contg. the NK1 receptor antagonist and GABA analog. The present invention also provides the use of an NK1 receptor antagonist and a GABA analog for the manuf. of a medicament for the treatment or prevention of psychiatric disorders. Synergistic interaction between oral gabapentin and CI1021 in isolation-induced vocalizations of guinea-pig pups was shown. A tablet contained CI1021 5, gabapentin 100, lactose 95, corn starch (for mix) 20, corn starch (paste) 20, and 1% magnesium stearate 10%.

ST pharmaceutical synergistic NK receptor antagonist GABA analog; tablet gabapentin CI1021 psychiatric disorder

IT Tachykinin receptors
(NK1 antagonists; pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

IT Anxiety
(panic disorder; pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

IT Drug delivery systems
(parenterals; pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

IT Antidepressants
Anxiolytics
Mental disorder
(pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

IT Mental disorder
(phobia, social; pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

IT Drug delivery systems
(solns., oral; pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

IT Drug delivery systems
(tablets; pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

IT 56-12-2D, GABA, analogs 60142-96-3, Gabapentin 148553-50-8, Pregabalin **158991-23-2, CI1021**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

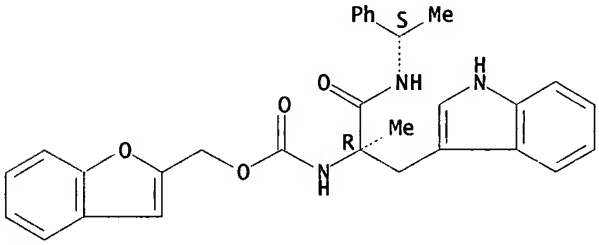
(1) Brown, J; US 5792796 A 1998 CAPLUS.
(2) Carlson Emma Joanne; WO 9815277 A 1998 CAPLUS
(3) Elliott Jason Matthew; WO 9824439 A 1998 CAPLUS
(4) Pande Atul, C; US 5510381 A 1996 CAPLUS
(5) Wallace Jan, D; US 5025035 A 1991 CAPLUS

IT **158991-23-2, CI1021**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. comprising synergistic combinations of NK1 receptor antagonist and GABA analog for treatment of psychiatric disorders)

RN 158991-23-2 CAPLUS

CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L23 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:536312 CAPLUS
DN 134:141620
TI Evaluation of selective NK1 receptor antagonist **CI-1021** in animal models of inflammatory and neuropathic pain
AU Gonzalez, Maria I.; Field, Mark J.; **Hughes, John**; **Singh, Lakhbir**
CS Parke-Davis Neuroscience Research Centre, Cambridge University, Cambridge, UK
SO Journal of Pharmacology and Experimental Therapeutics (2000), 294(2), 444-450
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
CC 1-11 (Pharmacology)
Section cross-reference(s): 2, 14
AB CI-1021 ([(2-benzofuran)-CH2OCO]-(R)-.alpha.-MeTrp-(S)-NHCH(CH3)Ph) is a selective and competitive neurokinin-1 (NK1) receptor antagonist. This study examines its activity in animal models of inflammatory and neuropathic pain. In mice, CI-1021 (1-30 mg/kg, s.c.) dose dependently blocked the development of the late phase of the formalin response with a min. ED (MED) of 3 mg/kg. Two chem. unrelated NK1 receptor antagonists, CP-99,994 (3-30 mg/kg) and SR 140333 (1-100 mg/kg), also dose dependently blocked the late phase, with resp. MEDs of 3 and 10 mg/kg. PD 156982, a NK1 receptor antagonist with poor central nervous system penetration, failed to have any effect. However, when administered i.c.v., it selectively blocked the late phase of the formalin response. Chronic constrictive injury (CCI) to a sciatic nerve in the rat induced spontaneous pain, thermal and mech. hyperalgesia, and cold, dynamic, and static allodynia. CI-1021 (10-100 mg/kg) and morphine (3 mg/kg) blocked all the responses except dynamic allodynia. Carbamazepine (100 mg/kg) was weakly effective against all the responses. Once daily administration of morphine (3 mg/kg, s.c.) in CCI rats led to the development of tolerance within 6 days. Similar administration of CI-1021 (100 mg/kg, s.c.) for up to 10 days did not induce tolerance. Moreover, the morphine tolerance failed to cross-generalize to CI-1021. CI-1021 blocked the CCI-induced hypersensitivity in the guinea pig, with a MED of 0.1 mg/kg, p.o. CI-1021 (10-100 mg/kg, s.c.) did not show sedative/ataxic action in the rat rota-rod test. It is suggested that NK1 receptor antagonists possess a superior side effect profile to carbamazepine and morphine and may have a therapeutic use for the treatment of inflammatory and neuropathic pain.
ST neurokinin receptor antagonist **CI1021** antiinflammatory antiallodynic; inflammation allodynia model NK receptor **CI1021**
IT Analgesia
Anti-inflammatory agents
Disease models
Inflammation

(CI-1021 in animal models of inflammatory and neuropathic pain)
IT Tachykinin receptors
(NK1 antagonists; CI-1021 in animal models of inflammatory and neuropathic pain)
IT Tachykinin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NK1; CI-1021 in animal models of inflammatory and neuropathic pain)
IT Pain
Skin, disease
(allodynia; CI-1021 in animal models of inflammatory and neuropathic pain)
IT 158991-23-2, CI-1021
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI-1021 in animal models of inflammatory and neuropathic pain)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Arner, S; Pain 1988, V33, P11 MEDLINE
(2) Bennett, G; Pain 1988, V33, P87 MEDLINE
(3) Block, G; Neurology 1998, V50, P225
(4) Choi, Y; Pain 1994, V59, P369 MEDLINE
(5) Coudore-Civiale, M; Eur J Pharmacol 1998, V361, P175 CAPLUS
(6) Cumberbatch, M; Neuropharmacology 1998, V37, P1535 CAPLUS
(7) Dickenson, A; Pain 1986, V24, P211 CAPLUS
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(20) Levine, J; Science (Wash DC) 1984, V226, P547 CAPLUS
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(27) Singh, L; Eur J Pharmacol 1997, V321, P209 CAPLUS
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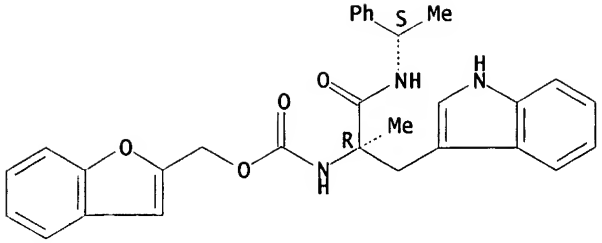
(29) Yamamoto, T; Neurosci Lett 1993, V161, P57 CAPLUS
(30) Yashpal, K; Brain Res 1990, V506, P259 CAPLUS
IT 158991-23-2, CI-1021
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI-1021 in animal models of inflammatory and neuropathic pain)
RN 158991-23-2 CAPLUS
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

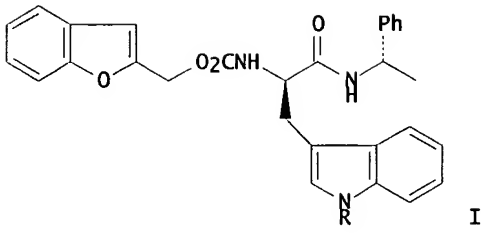
Absolute stereochemistry.



L23 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:672811 CAPLUS
DN 131:299365
TI Preparation of prodrugs of benzofuranylmethyl carbamate NK1 antagonists
IN Chan, Oilun Helen; Chen, Michael Huai Gu; Goel, Om Prakash; Hershenson, Fred M.; Zhu, Zhijian
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D405-12
ICS A61K031-405; A61K031-34; A61K031-675; C07F009-141; C07F009-145; C07F009-22
CC 27-11 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9952903	A1	19991021	WO 1999-US6041	19990319 <--
	W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2323047	AA	19991021	CA 1999-2323047	19990319 <--
	AU 9930114	A1	19991101	AU 1999-30114	19990319 <--
	EP 1075472	A1	20010214	EP 1999-911477	19990319 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002511467	T2	20020416	JP 2000-543460	19990319 <--
	US 6258800	B1	20010710	US 2000-601570	20000803 <--
PRAI	US 1998-81881P	P	19980415 <--		
	WO 1999-US6041	W	19990319 <--		

OS MARPAT 131:299365
GI



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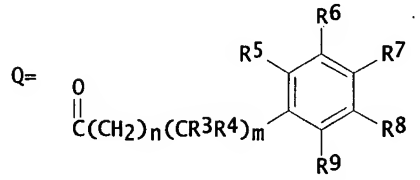

AB Aq. sol. prodrugs I [R = CH2OZ, C(O)OCH2OZ, Z, wherein Z = Q, P(O)(OH)2, C(O)Q1; n = 0-3; m = 0, 1] of certain tachykinin antagonists (NK1 antagonists) useful in the treatment of emesis, were prepd. E.g., {3-[2-(benzofuran-2-ylmethoxycarbonylamino)-2-(1-phenylethylcarbamoyl)propyl]indol-1-yl}phosphonic acid disodium salt was prepd.

ST benzofuranylmethyl carbamate NK1 antagonist prodrug prepn

IT Tachykinin receptors
(NK1 antagonists; prepn. of prodrugs of benzofuranylmethyl carbamate NK1 antagonists)

IT 247017-84-1P 247017-93-2P 247018-00-4P 247018-10-6P 247018-11-7P 247018-12-8P 247018-13-9P 247042-05-3P 247042-06-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of prodrugs of benzofuranylmethyl carbamate NK1 antagonists)

IT 103-76-4, 1-Piperazineethanol 109-01-3, N-Methylpiperazine 110-85-0, Piperazine, reactions 110-91-8, Morpholine, reactions 111-42-2, reactions 142-25-6, N,N,N'-Trimethylethylenediamine 538-37-4 543-27-1, Isobutyl chloroformate 619-66-9, 4-Carboxybenzaldehyde 1138-80-3 1642-81-5 50651-75-7 86070-82-8, 3-Hydroxypyrrolidine hydrochloride 153910-62-4 **158991-23-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of prodrugs of benzofuranylmethyl carbamate NK1 antagonists)

IT 34040-64-7P 69704-08-1P 94224-92-7P 247017-82-9P 247017-83-0P 247017-85-2P 247017-86-3P 247017-87-4P 247017-89-6P 247017-90-9P 247017-91-0P 247017-92-1P 247017-94-3P 247017-96-5P 247017-97-6P 247017-98-7P 247017-99-8P 247018-02-6P 247018-03-7P 247018-04-8P 247018-06-0P 247018-07-1P 247018-08-2P 247018-17-3P 247018-18-4P 247018-19-5P 247018-20-8P 247018-21-9P 247018-22-0P 247018-23-1P 247018-24-2P 247018-25-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of prodrugs of benzofuranylmethyl carbamate NK1 antagonists)

IT 247017-81-8P 247017-88-5P 247017-95-4P 247018-05-9P 247018-09-3P 247018-14-0P 247018-15-1P 247018-16-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of prodrugs of benzofuranylmethyl carbamate NK1 antagonists)

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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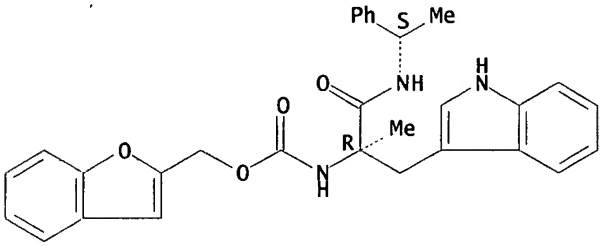
IT **158991-23-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of prodrugs of benzofuranylmethyl carbamate NK1 antagonists)
RN 158991-23-2 CAPLUS
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L23 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:275762 CAPLUS
DN 129:12660
TI Evaluation of **PD 154075**, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain
AU Gonzalez, M. Isabel; Field, Mark J.; Holloman, Elizabeth F.; **Hughes, John**; Oles, Ryszard J.; **Singh, Lakhbir**
CS Department of Biology, Cambridge University Forvie Site, Cambridge, CB2 2QB, UK
SO European Journal of Pharmacology (**1998**), 344(2/3), 115-120
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-11 (Pharmacology)
AB PD 154075 ([(2-benzofuran)-CH2OCO]-(R)-.alpha.-MeTrp-(S)-NHCH(CH3)Ph) is a selective tachykinin NK1 receptor antagonist. Its effect on development and maintenance of thermal and mech. hypersensitivity was examd. in a rat model of surgical pain. When administered 30 min before surgery, PD 154075 dose-dependently (3-100 mg/kg, s.c.) prevented the development of thermal and mech. hypersensitivity with resp. min. EDs of 10 and 30 mg/kg. These antihypersensitivity effects lasted for 72 h. In contrast, the administration of PD 154075 (30 mg/kg, s.c.) after surgery had little or no effect on these nociceptive responses. PD 154075 antagonized thermal hypersensitivity induced by intrathecal administration of substance P, over the same dose range that blocked surgical hypersensitivity. However, it only partially blocked the thermal hypersensitivity induced by the selective NK2 receptor agonist [.beta.-Ala8]neurokinin A-(4-10). Morphine dose-dependently (1-6 mg/kg, s.c.) lengthened isoflurane and pentobarbitone-induced sleeping time in the rat. In contrast, PD 154075 (3-100 mg/kg, s.c.) did not interact with these anesthetics. It is suggested that tachykinin NK1 receptor antagonists, such as PD 154075, may possess therapeutic potential as pre-emptive antihypersensitive agents.
ST **PD 154075** NK1 antagonist surgery pain
IT Tachykinin receptors
(NK1 antagonists; evaluation of **PD 154075**, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain)
IT Analgesics
(evaluation of **PD 154075**, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain)
IT Surgery

(postsurgical pain; evaluation of **PD 154075**, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain)

IT 33507-63-0, Substance P (peptide) 122063-01-8, [.beta.-Ala8]neurokinin A-(4-10)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(evaluation of **PD 154075**, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain)

IT **158991-23-2, PD 154075**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of **PD 154075**, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain)

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Atweh, S; Brain Res 1977, V124, P53 CAPLUS
(2) Boyle, S; Bio Med Chem 1994, V2, P357 CAPLUS
(3) Brennan, T; Pain 1996, V64, P493 MEDLINE
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(9) Levine, J; Science 1984, V226, P547 CAPLUS
(10) Ma, Q; J Physiol 1995, V486, P769 CAPLUS
(11) Maggi, C; J Autonom Pharmacol 1993, V13, P23 CAPLUS
(12) Rupniak, N; Pain 1996, V67, P189 CAPLUS
(13) Seguin, L; Pain 1995, V61, P325 CAPLUS
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(20) Yamamoto, T; Neurosci Lett 1993, V161, P57 CAPLUS
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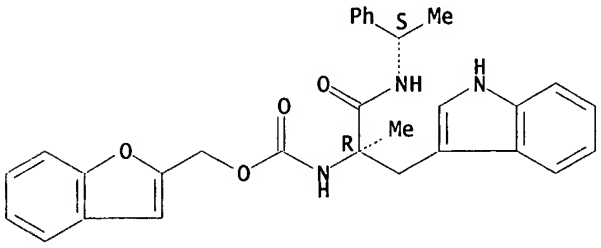
IT **158991-23-2, PD 154075**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of **PD 154075**, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain)

RN 158991-23-2 CAPLUS

CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L23 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1998:42272 CAPLUS

DN 128:97714

TI Use of a tachykinin antagonist, [R,S]-[2-(1H-Indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester, for the manufacture of a medicament for the treatment of emesis

IN Horwell, David Christopher; Hugues, John; Pritchard, Martyn Clive; **Singh, Lakhbir**

PA Warner-Lambert Co., USA; Horwell, David Christopher; Hugues, John; Pritchard, Martyn Clive; Singh, Lakhbir

SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-40

CC 1-9 (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9749393	A1	19971231	WO 1997-US10503	19970618 <--
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9735718	A1	19980114	AU 1997-35718	19970618 <--
	AU 714542	B2	20000106		
	EP 912173	A1	19990506	EP 1997-932196	19970618 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
	NZ 333062	A	20000623	NZ 1997-333062	19970618 <--
	JP 2000514047	T2	20001024	JP 1998-503257	19970618 <--
	ZA 9705637	A	19980123	ZA 1997-5637	19970625 <--
	US 5998435	A	19991207	US 1998-194620	19981201 <--
PRAI	US 1996-21030P	P	19960626 <--		
	WO 1997-US10503	W	19970618 <--		

AB A method is provided for the treatment of emesis, comprising administering a compd. named [R,S]-[2-(1H-Indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester.

ST tachykinin antagonist carbamate deriv emesis treatment

IT 5-HT receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(5-HT3; tachykinin antagonist carbamate deriv. for emesis treatment)

IT Tachykinin receptors
(NK1 antagonists; tachykinin antagonist carbamate deriv. for emesis treatment)

IT Antitumor agents
(emesis induced by; tachykinin antagonist carbamate deriv. for emesis treatment)

IT Surgery
(nausea after; tachykinin antagonist carbamate deriv. for emesis treatment)

IT Brain
(penetration; tachykinin antagonist carbamate deriv. for emesis treatment)

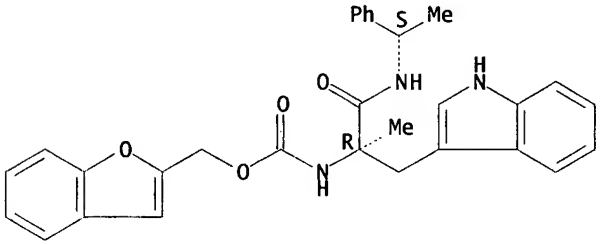
IT Nausea
(post-operative; tachykinin antagonist carbamate deriv. for emesis treatment)

IT Antiemetics
Drug bioavailability
Motion sickness
Pharmacokinetics
(tachykinin antagonist carbamate deriv. for emesis treatment)

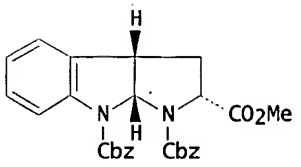
IT 15663-27-1, Cisplatin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(emesis induced by; tachykinin antagonist carbamate deriv. for emesis

treatment)
IT **158991-23-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(tachykinin antagonist carbamate deriv. for emesis treatment)
IT 99614-02-5, Ondansetron
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tachykinin antagonist carbamate deriv. for emesis treatment, and comparison with ondansetron)
IT **158991-23-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(tachykinin antagonist carbamate deriv. for emesis treatment)
RN 158991-23-2 CAPLUS
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L23 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:801039 CAPLUS
DN 128:75654
TI Tetrahydropyrrolo[2,3-b]indole-1,2,8-tricarboxylic acid ester in the enantiospecific preparation of .alpha.-methyltryptophan: application in the preparation of carbon-14 labeled PD 145942 and **PD 154075**
AU Ekhato, I. Victor; Huang, Yun
CS Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company, Department of Chemical Development, Ann Arbor, MI, 48105, USA
SO Journal of Labelled Compounds & Radiopharmaceuticals (**1997**), 39(12), 1019-1038
CODEN: JLCRD4; ISSN: 0362-4803
PB John Wiley & Sons Ltd.
DT Journal
LA English
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
OS CASREACT 128:75654
GI



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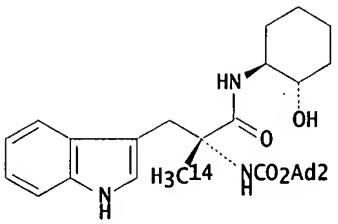
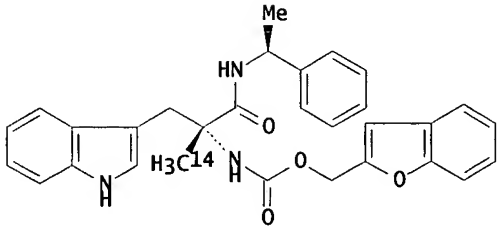


II



III

AB [2R-(2.alpha., 3a.beta., 8a.beta.)]-2,3,3a,8a-Tetrahydro-pyrrolo[2,3-b]indole-1,2,8-tricarboxylic acid-1,8-dibenzyl ester 2-Me ester (I), its [2S-(2.beta., 3a.alpha., 8a.alpha.)]-isomer, and the tribenzyl ester analogs were prepd. From these [2,3-b]indole-1,2,8-tricarboxylic acid esters we accomplished a simple, high yielding prepn. of enantiopure .alpha.-methyltryptophan and Me ester derivs. Using this protocol, we inexpensively made (R)-.alpha.-[14C]methyltryptophan Me ester, and in subsequent reactions converted it into PD 145942, II (Ad2 = 2-adamantyl) and PD 154075, III. Both of these compds. are drug candidates in preclin. study for the treatment of anxiety and emesis resp.

ST labeled CCKB receptor antagonist PD145942 prepn; NK1 receptor antagonist labeled **PD154075** prepn; asym synthesis labeled methyltryptophan; stereoselective alkylation tryptophan pyrroloindole

IT Asymmetric synthesis and induction
Stereochemistry
(prepn. of methyltryptophan and its application in the prepn. of labeled PD 145942 and **PD 154075**)

IT Alkylation
(stereoselective; of tetrahydropyrroloindole tricarboxylic acid ester in the enantiospecific prepn. of methyltryptophan)

IT 501-53-1, Benzyl chloroformate 2279-15-4, N-Benzyloxycarbonyl-D-tryptophan 2627-86-3 7432-21-5, N-Benzyloxycarbonyl-L-tryptophan 16170-82-4 53120-53-9, 2-Adamantyl chloroformate 74111-21-0 158951-87-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of methyltryptophan and its application in the prepn. of labeled PD 145942 and **PD 154075**)

IT 126496-81-9P 152876-57-8P 169687-65-4P 200716-86-5P 200716-87-6P 200716-88-7P 200716-90-1P 200716-91-2P 200716-92-3P 200716-93-4P 200716-95-6P 200716-96-7P 200716-97-8P 200716-98-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of methyltryptophan and its application in the prepn. of labeled PD 145942 and **PD 154075**)

IT 16709-25-4P 56452-52-9P 142854-50-0P 200716-89-8P 200716-94-5P 200716-99-0P 200717-00-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of methyltryptophan and its application in the prepn. of labeled PD 145942 and **PD 154075**)

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Bourne, G; J Chem Soc, Perkin Trans 1 1991, P1693 CAPLUS
(2) Boyle, S; Bioorganic & Med Chem 1994, V2(5), P357 CAPLUS
(3) Brana, M; J Heterocycles 1980, V17, P829 CAPLUS

(4) Burgaud, B; Tetrahedron Asymmetry 1995, V6(5), P1081 CAPLUS
(5) Cativiela, C; Synlett 1994, P302 CAPLUS
(6) Ekhato, I; Intl Isotope Society, Ninth Central US Meeting Chicago, III 1996
(7) Liedtke, B; Parke-Davis internal communication
(8) Plenevaux, A; Appl Radiat Isot 1994, V45(6), P651 CAPLUS
(9) Singh, L; Eur J Pharmacol 1997, V321, P209 CAPLUS
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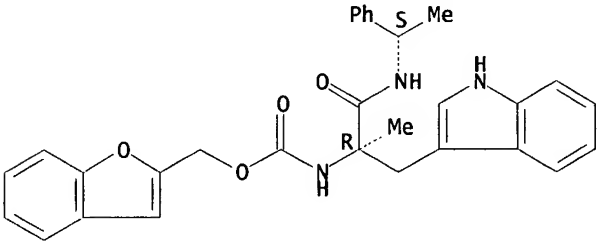
(11) Trivedi, B; J Med Chem In press
(12) Venkatachalam, T; J Labelled Compd Radiopharm 1993, V33(11), P1029 CAPLUS
(13) Zhang, L; J Org Chem 1995, V60, P5719 CAPLUS

L23 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:181574 CAPLUS
DN 126:258877
TI The tachykinin NK1 receptor antagonist **PD 154075** blocks cisplatin-induced delayed emesis in the ferret
AU **Singh, Lakhbir**; Field, Mark J.; **Hughes, John**; Kuo, Be-Sheng; Suman-Chauhan, Nirmala; Tuladhar, Bishwa R.; Wright, D. Scott; Naylor, Robert J.
CS Dep. Biology, Cambridge Univ. Forvie Site, Robinson Way, Cambridge, CB2 2QB, UK
SO European Journal of Pharmacology (**1997**), 321(2), 209-216
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier
DT Journal
LA English
CC 1-9 (Pharmacology)
AB The activity of a selective tachykinin NK1 receptor antagonist, PD 154075 ([(2-benzofuran)-CH2OCO]-(R)-.alpha.-MeTrp-(S)-NHCH(CH3)Ph), was examd. in radioligand binding studies, in a [Sar9,Met(O2)11]substance P-induced foot-tapping model in the gerbil, and in cisplatin-induced acute and delayed emesis in the ferret. In radioligand binding studies, PD 154075 showed nanomolar for the human, guinea-pig, gerbil, dog and ferret NK1 receptors with an approx. 300 times lower affinity for the rodent NK1 receptor. Using NK2, NK3 receptors and a range of other receptor ligands, PD 15407 was shown to exhibit a high degree of selectivity and specificity for the human type NK1 receptor. Following s.c. administration PD 154075 dose dependently (1-100 mg/kg) antagonized the centrally mediated [Sar9,Meet(O2)11] substance P-induced foot tapping in the gerbil with a min. ED (MED) of 100 mg/kg. The ability of PD 154075 to readily penetrate into the brain following oral administration was confirmed by its extn. and high performance liq. chromatog. assay from the rat brain. PD 154075 was shown to achieve a relatively fast and sustained brain concn. (brain/plasma ratios ranged from 0.27 to 0.41 during the time period of 0.25-12 h). Further pharmacokinetic studies revealed that the abs. oral bioavailability of PD 154075 in the rat was (mean .+-. S.D.) 49 .+-. 15%. PD 154075 (1-30 mg/kg, i.p.) dose dependently antagonized the acute vomiting and retching in the ferret measured for 4 h following administration of cisplatin (10 mg/kg, i.p.) with a MED of 3 mg/kg. The administration of a lower dose of cisplatin (5 mg/kg, i.p.) in the ferret induces both an acute (day 1) and delayed (days 2 and 3) phase of emesis. The i.p. administration of PD 154075, 10 mg/kg three times a days for 3 days, almost completely blocked both the acute and delayed emetic responses. In the same study, the 5-HT3 receptor antagonist ondansetron (1 mg/kg, i.p., t.i.d.) was also very effective against the acute emetic response obsd. during the first 4 h following cisplatin, but it was only weakly active against the delayed response. In conclusion, PD 154075 is a selective and specific high affinity NK1 receptor antagonist with good oral bioavailability which is effective against both acute and delayed emesis induced by cisplatin in the ferret.
ST **PD154075** antiemetic cisplatin tachykinin NK1 antagonist
IT Tachykinin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NK1; tachykinin NK1 receptor antagonist **PD 154075** prevention of cisplatin-induced delayed emesis)
IT Brain

(antiemetic **PD 154075** penetration into brain)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tachykinin NK1 receptor antagonist **PD 154075** affinity for various receptors)
IT Antiemetics
(tachykinin NK1 receptor antagonist **PD 154075** prevention of cisplatin-induced delayed emesis)
IT 15663-27-1, Cisplatin
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(tachykinin NK1 receptor antagonist **PD 154075** prevention of cisplatin-induced delayed emesis)
IT **158991-23-2, PD 154075**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tachykinin NK1 receptor antagonist **PD 154075** prevention of cisplatin-induced delayed emesis)
IT **158991-23-2, PD 154075**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tachykinin NK1 receptor antagonist **PD 154075** prevention of cisplatin-induced delayed emesis)
RN 158991-23-2 CAPLUS
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



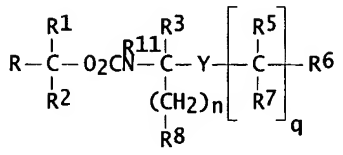
L23 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:70361 CAPLUS
DN 126:171893
TI Preparation of tryptophan derivatives as tachykinin antagonists
IN Horwell, David C.; Howson, William; Pritchard, Martyn C.; Roberts, Edward; Rees, David C.
PA Warner-Lambert Company, USA
SO U.S., 54 pp., Cont.-in-part of U.S. Ser. No. 97, 264, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D209-12
ICS C07D403-12; C07D407-12; A61K031-40
NCL 514419000
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 2, 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5594022	A	19970114	US 1994-344064	19941129 <--
	EP 1000930	A2	20000517	EP 2000-102502	19930812 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	ES 2153841	T3	20010316	ES 1993-919974	19930812 <--

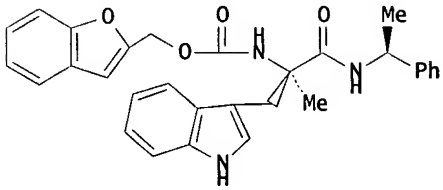
	US 5716979	A	19980210	US 1996-727067	19961008 <--	
	US 5856354	A	19990105	US 1997-953037	19971017 <--	
	US 5981755	A	19991109	US 1998-168512	19981008 <--	
PRAI	US 1992-930252	B2	19920813 <--			
	US 1993-97264	B2	19930723 <--			
	EP 1993-919974	A3	19930812 <--			
	US 1994-344064	A3	19941129 <--			
	US 1996-727067	A3	19961008 <--			
	US 1997-953037	A3	19971017 <--			

OS MARPAT 126:171893

GI



I



II

AB The invention concerns tachykinin antagonists I [R, R6, R8 = independently Ph, pyridine, thiophene, furan, naphthalene, indole, benzofuran, or benzothiophene optionally substituted with 1-3 alkyl, OH, alkoxy, NO2, halo, NH2, CF3, C1-8 straight alkyl, C3-8 branched alkyl, C5-8 cycloalkyl, heterocycloalkyl; R, R2 = independently H, C1-4 alkyl; R and R2 can also form a ring; R3 = H, (CH2)mR13; Y = COR4, CO2, COCH2, CH2O, CH2NH, CH:CH, CH2CH2, CH(OH)CH2, heterocyclic residue; R4, R11 = independently H, C1-3 alkyl; R5, R7 = independently H, C1-4 alkyl; R13 = H, CN, NH2, NMe2, NHAc; m = 1-6; n = 1-2; q = 0, 1], nonpeptides which have utility in treating disorders mediated by tachykinins, such as respiratory, inflammatory, gastrointestinal, ophthalmic and vascular disorders, allergies, pain, diseases of the central nervous system, and migraine. Methods of prepg. compds. I and novel intermediates are also included. The compds. I are expected to be esp. useful in asthma and rheumatoid arthritis. Thus, treatment of .alpha.-methyltryptophanyl 1-phenethylamide (prepn. given) with 2-benzofuranylmethyl 4-nitrophenyl carbonate (prepn. given) gave 56% tryptophan amide II. II exhibited IC50 = 9 nm in an in vitro neurokinin 1 (NK1) receptor binding assay, while related derivs. showed IC50 = 19 to >10,000 nM. II and related compds. were also active in vivo as NK1 receptor antagonists (ID50 = 2.8 to 0.0024 mg/kg IV).

ST tryptophan amide prepn tachykinin antagonist; neurokinin receptor antagonist tryptophan amide prepn; asthma treatment tryptophan amide prepn; rheumatoid arthritis treatment tryptophan amide prepn

IT Tachykinin receptors
(NK1 antagonists; prepn. of tryptophan derivs. as tachykinin antagonists)

IT Tachykinins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antagonists; prepn. of tryptophan derivs. as tachykinin antagonists)

IT Antiasthmatics
Antirheumatic agents
(prepn. of tryptophan derivs. as tachykinin antagonists)

IT 158951-79-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of tryptophan derivs. as tachykinin antagonists)

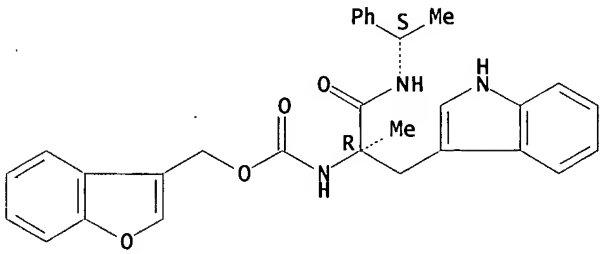
IT 158951-68-9P 158951-71-4P 158951-72-5P 158951-73-6P 158951-74-7P
158951-75-8P 158951-76-9P 158951-77-0P 158951-78-1P 158951-80-5P
159672-27-2P 159672-28-3P 159672-30-7P 159672-31-8P 159672-33-0P
159672-34-1P 159672-35-2P 159672-36-3P 159672-37-4P 159672-38-5P
159672-39-6P 159672-40-9P 159672-41-0P 159672-42-1P 159672-43-2P
159672-44-3P 159672-48-7P 159672-49-8P 159672-50-1P 159672-51-2P
159672-54-5P 159672-55-6P 159672-56-7P 159672-58-9P 159672-59-0P
159672-60-3P 159672-61-4P 159672-62-5P 159672-63-6P 159672-64-7P
159672-65-8P 159672-66-9P 159672-69-2P 159672-70-5P 159672-71-6P
159672-73-8P 159672-98-7P **169475-89-2P** 169475-96-1P
187085-26-3P 187085-27-4P 187085-28-5P 187085-29-6P 187085-38-7P
187085-40-1P 187085-42-3P 187085-45-6P 187085-46-7P 187085-49-0P
187085-60-5P 187085-62-7P 187085-67-2P 187085-69-4P 187085-71-8P
187085-74-1P 187085-75-2P 187085-77-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of tryptophan derivs. as tachykinin antagonists)

IT 63-84-3, DL-3,4-Dihydroxyphenylalanine 98-00-0, 2-Furanmethanol
98-85-1, (RS)-sec-Phenethyl alcohol 100-46-9, Benzylamine, reactions
103-67-3, N-Methylbenzylamine 104-86-9, 4-Chlorobenzylamine 105-13-5,
4-Methoxybenzyl alcohol 122-00-9 147-71-7 154-08-5,
5-Fluoro-DL-tryptophan 321-12-0, 2-Fluoro-5-methylbenzoic acid
349-95-1, 4-Trifluoromethylbenzyl alcohol 446-51-5, 2-Fluorobenzyl alcohol 456-47-3, 3-Fluorobenzyl alcohol 459-56-3, 4-Fluorobenzyl alcohol 496-41-3, Benzofuran-2-carboxylic acid 526-30-7, Tryptazan
526-31-8, Abrine 589-18-4, 4-Methylbenzyl alcohol 590-17-0,
Bromoacetonitrile 618-36-0, (RS)-.alpha.-Methylbenzylamine 636-72-6,
2-Thiophenemethanol 873-76-7, 4-Chlorobenzyl alcohol 1122-54-9,
4-Acetylpyridine 1592-38-7, 2-Naphthalenemethanol 2217-40-5,
1,2,3,4-Tetrahydro-1-naphthylamine 2627-86-3, (S)-.alpha.-Methylbenzylamine 3173-56-6, Benzyl isocyanate 3300-51-4,
4-Trifluoromethylbenzylamine 3392-11-8, BOC-Trp-OSu 3886-69-9,
(R)-.alpha.-Methylbenzylamine 4254-29-9 4412-91-3, 3-Furanmethanol
5913-13-3, (R)-1-Cyclohexylethylamine 6298-96-0 6299-02-1,
4-Chloro-.alpha.-methylbenzylamine 6351-10-6, 1-Hydroxyindane
7303-49-3, DL-Tryptophan methyl ester 7693-46-1, 4-Nitrophenyl chloroformate 13058-16-7 14091-15-7, DL-4-Bromophenylalanine
17543-50-9 17890-56-1, Benzo[b]thiophene-2-methanol 26988-72-7,
1-Methyl-DL-tryptophan 32707-89-4, 3,5-Bis(trifluoromethyl)benzyl alcohol 32919-24-7 56456-47-4, 2,4-Difluorobenzyl alcohol
71637-34-8, 3-Thiophenemethanol 75853-18-8, 2,3-Difluorobenzyl alcohol
75853-20-2, 2,5-Difluorobenzyl alcohol 76985-09-6 96551-27-8
114524-80-0 158276-69-8 159672-76-1 159672-79-4 159672-88-5
159672-90-9 187085-78-5 187085-81-0 187085-97-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of tryptophan derivs. as tachykinin antagonists)

IT 1194-99-6P, 4-Acetylpyridine oxime 1881-79-4P 2089-33-0P 4687-23-4P,
3-Benzofuranmethanol 7424-00-2P 16108-04-6P 21658-36-6P
25506-37-0P 27854-96-2P 32063-45-9P 53761-06-1P 64977-30-6P
82611-57-2P 97534-88-8P 97557-59-0P 112913-63-0P 130245-37-3P
130270-23-4P 141037-13-0P 141971-07-5P 141971-19-9P 143218-10-4P
144186-68-5P 146953-09-5P 158276-62-1P 158951-84-9P 158951-85-0P
158951-86-1P 158951-87-2P 159672-78-3P 159672-80-7P 159672-81-8P
159672-82-9P 159672-83-0P 159672-84-1P 159672-85-2P 159672-86-3P
159672-87-4P 159672-89-6P 159672-91-0P 159672-94-3P 159672-95-4P
159672-96-5P 159672-97-6P 166519-65-9P 169673-44-3P 183161-56-0P
187085-98-9P 187086-06-2P 187086-07-3P 187086-08-4P 187086-09-5P
187086-10-8P 187086-11-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of tryptophan derivs. as tachykinin antagonists)

IT **169475-89-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of tryptophan derivs. as tachykinin antagonists)
RN 169475-89-2 CAPLUS
CN Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 3-benzofuranylmethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L23 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:407860 CAPLUS
DN 125:184873
TI 'Targeted' molecular diversity: design and development of non-peptide antagonists for cholecystokinin and tachykinin receptors
AU Horwell, David; Pritchard, Martyn; Raphy, Jennifer; Ratcliffe, Giles
CS Parke-Davis Neuroscience Research Centre, The Forvie Site, Robinsin Way, Cambridge, CB2 2QB, UK
SO Immunopharmacology (**1996**), 33(1-3, Papers presented at KININ '95, Fourteenth International Symposium on Bradykinin and Related Kinins, 1995), 68-72
CODEN: IMMUDP; ISSN: 0162-3109
PB Elsevier
DT Journal
LA English
CC 1-3 (Pharmacology)
AB A drug design strategy to non-peptide small mol. antagonists of neuropeptides is described that targets the mol. diversity which exists in the 'privileged' data set of the physico-chem. properties represented by the side-chains of the 20 genetically encoded amino acids. The strategy is exemplified by the design of a selective and high affinity cholecystokinin CCK-A antagonist PD 140548, CCK-B antagonist CI-988 (formerly PD 134308) tachykinin NK-1 antagonist PD 154075 and NK-2 antagonist Cam-2291. The NK-3 antagonists, PD 157672 and the non-peptide PD 161182, were developed from an information-rich dipeptide library constructed from 256 N-protected dipeptides and 64 hydrophobic biased dipeptides.
ST drug design nonpeptide cholecystokinin tachykinin antagonist
IT Pharmaceuticals
(design; design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cholecystokinin, design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)
IT Kinin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tachykinin, design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)
IT Kinin receptors
Receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tachykinin NK1, design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)

IT Kinin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tachykinin NK2, design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)

IT Kinin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tachykinin NK3, design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)

IT Kinins (animal hormones)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tachykinins, design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)

IT 130404-91-0, PD 134308 140677-01-6, PD 140548 158276-60-9, Cam 2291
158991-23-2, PD 154075 159698-59-6, PD
157672 168570-35-2, Pd 161182
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)

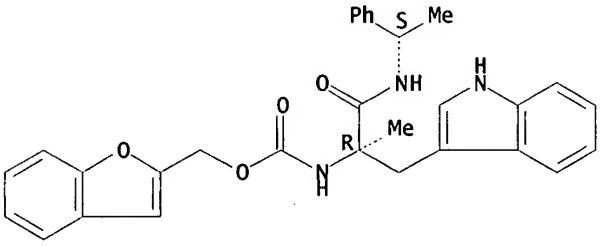
IT 9011-97-6, Cholecystokinin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)

IT **158991-23-2, PD 154075**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(design and development of nonpeptide antagonists for cholecystokinin and tachykinin receptors)

RN 158991-23-2 CAPLUS

CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L23 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN

AN 1995:849921 CAPLUS

DN 123:275215

TI Quantitative Structure-Activity Relationships (QSARs) of N-Terminus Fragments of NK1 Tachykinin Antagonists: A Comparison of Classical QSARs and Three-Dimensional QSARs from Similarity Matrixes

AU Horwell, David C.; Howson, William; Higginbottom, Michael; Naylor, Dorica; Ratcliffe, Giles S.; Williams, Sophie

CS Parke-Davis Neuroscience Research Centre, Cambridge University Forvie Site, Cambridge, CB2 2QB, UK

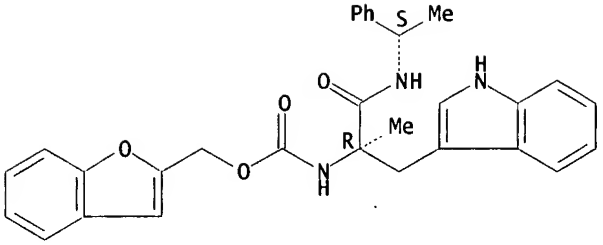
SO Journal of Medicinal Chemistry (1995), 38(22), 4454-62
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

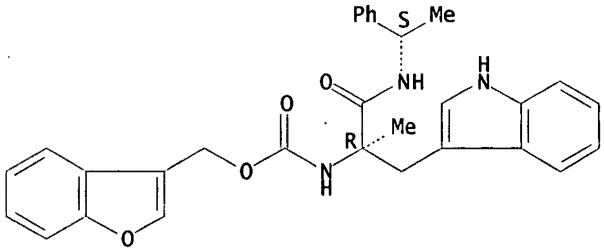
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 27
AB The ability of three-dimensional quant. structure-activity relationships (QSARs) derived from classical QSAR descriptors and similarity indexes to rationalize the activity of 28 N-terminus fragments of tachykinin NK1 receptor antagonists was examd. Two different types of analyses, partial least squares and multiple regression, were performed in order to check the robustness of each derived model. The models derived using classical QSAR descriptors lacked accurate quant. and predictive abilities to describe the nature of the receptor-inhibitor interaction. However models derived using 3D QSAR descriptors based on similarity indexes were both robust and significantly predictive. The best model was obtained through the statistical anal. of mol. field similarity indexes (n = 28, r2 = 0.846, r(cv)2 = 0.737, s = 0.987, PRESS = 7.102) suggesting that electronic and size-related properties are the most relevant in explaining the affinity data of the training set. The overall quality and predictive ability of the models applied to the test set appear to be very high, since the predicted affinities of three test compds. agree with the exptl. detd. affinities obtained subsequently within the exptl. error of the binding data.
ST tachykinin antagonist structure QSAR model
IT Quantitative structure-activity relationship
(models for QSAR study of NK1 tachykinin antagonists)
IT Kinin receptors
Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tachykinin NK1, antagonists; models for QSAR study of NK1 tachykinin antagonists)
IT Molecular structure-biological activity relationship
(tachykinin-inhibiting, models for QSAR study of NK1 tachykinin antagonists)
IT 158951-79-2P **158991-23-2P** 159672-34-1P 159672-35-2P
159672-36-3P 159672-59-0P 159672-65-8P 159672-66-9P 159672-98-7P
169475-69-8P 169475-70-1P 169475-71-2P 169475-72-3P 169475-73-4P
169475-74-5P 169475-75-6P 169475-76-7P 169475-77-8P 169475-78-9P
169475-79-0P 169475-80-3P 169475-81-4P 169475-82-5P 169475-83-6P
169475-84-7P 169475-85-8P 169475-86-9P 169475-87-0P 169475-88-1P
169475-89-2P 169475-90-5P 169475-91-6P 169475-92-7P
169475-93-8P 169475-94-9P 169475-95-0P 169475-96-1P 169475-97-2P
169475-98-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(models for QSAR study of NK1 tachykinin antagonists)
IT **158991-23-2P 169475-89-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(models for QSAR study of NK1 tachykinin antagonists)
RN 158991-23-2 CAPLUS
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

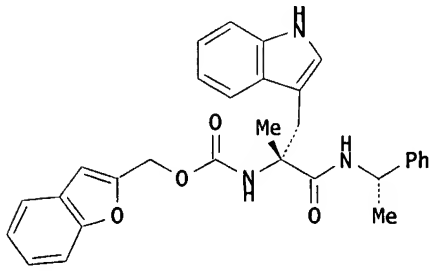


RN 169475-89-2 CAPLUS
CN Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 3-benzofuranylmethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L23 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1994:681116 CAPLUS
DN 121:281116
TI Rational design of high affinity tachykinin NK1 receptor antagonists
AU Boyle, Steven; Guard, Steven; Higginbottom, Michael; Horwell, David C.; Howson, William; McKnight, Alexander; Martin, Kevan; Pritchard, Martyn C.; O'Toole, John; et al.
CS Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Cambridge, CB2 2QB, UK
SO Bioorganic & Medicinal Chemistry (1994), 2(5), 357-70
CODEN: BMECEP; ISSN: 0968-0896
DT Journal
LA English
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 2
GI



I

AB The rational design of a nonpeptide tachykinin NK1 receptor antagonist I (PD 154075) is described. I has Ki = 9 and 0.35 nM for the NK1 receptor

binding site in guinea pig cerebral cortex membranes and human IM9, cells resp. (using [125I] Bolton-Hunger-SP as the radioligand). It is a potent antagonist in vitro where it antagonizes the contractions mediated by SPOMe in the guinea-pig ileum (KB = 0.3 nM). I is active in vivo in the guinea pig plasma extravasation model, where it is able to block the SPOMe-induced protein plasma extravasation (monitored by Evans Blue) in the bladder with an ID50 of 0.02 mg kg-1 i.v.

ST nonpeptide tachykinin antagonist **PD 154075**; benzofuranylmethyltryptophan methylbenzylamide tachykinin receptor antagonist; tryptophanamide benzofuranylmethyl tachykinin receptor antagonist

IT Kinin receptors
Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tachykinin NK1, antagonists; rational design of high affinity tachykinin NK1 receptor antagonists)

IT Molecular structure-biological activity relationship
(tachykinin-inhibiting, rational design of high affinity tachykinin NK1 receptor antagonists)

IT 20695-94-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(rational design of high affinity tachykinin NK1 receptor antagonists)

IT 158276-61-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(rational design of high affinity tachykinin NK1 receptor antagonists)

IT 158951-57-6P 158951-58-7P 158951-59-8P 158951-60-1P 158951-61-2P
158951-62-3P 158951-63-4P 158951-64-5P 158951-65-6P 158951-66-7P
158951-67-8P 158951-68-9P 158951-69-0P 158951-70-3P 158951-71-4P
158951-72-5P 158951-73-6P 158951-74-7P 158951-75-8P 158951-76-9P
158951-77-0P 158951-78-1P 158951-79-2P 158951-80-5P 158951-81-6P
158991-23-2P, PD 154075
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(rational design of high affinity tachykinin NK1 receptor antagonists)

IT 62-53-3, Aniline, reactions 64-04-0, 2-Phenylethylamine 100-46-9, Benzylamine, reactions 830-96-6, 1H-Indole-3-propionic acid 1445-91-6, (S)-1-Phenylethanol 1517-69-7, (R)-1-Phenylethanol 1592-38-7, 2-Naphthalenemethanol 2279-15-4, N-Benzyloxycarbonyl-D-tryptophan 2627-86-3, (S)-.alpha.-Methylbenzylamine 3886-69-9, (R)-.alpha.-Methylbenzylamine 5241-58-7, (S)-Phenylalaninamide 7432-21-5, N-Benzyloxycarbonyltryptophan 17543-50-9 41222-70-2, D-Tryptophan methyl ester hydrochloride 55038-01-2, 2-Benzofuranmethanol 86069-87-6 96551-27-8 110884-69-0 136554-94-4 158276-62-1 158951-86-1 158951-87-2 158951-88-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(rational design of high affinity tachykinin NK1 receptor antagonists)

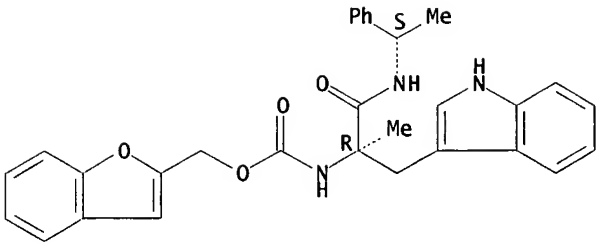
IT 125009-81-6P 158951-82-7P 158951-83-8P 158951-84-9P 158951-85-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(rational design of high affinity tachykinin NK1 receptor antagonists)

IT **158991-23-2P, PD 154075**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(rational design of high affinity tachykinin NK1 receptor antagonists)

RN 158991-23-2 CAPLUS

CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Oct 2003 (20031023/PD)
FILE LAST UPDATED: 23 Oct 2003 (20031023/ED)
HIGHEST GRANTED PATENT NUMBER: US6637033
HIGHEST APPLICATION PUBLICATION NUMBER: US2003200588
CA INDEXING IS CURRENT THROUGH 23 Oct 2003 (20031023/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Oct 2003 (20031023/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2003

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d l24 tot bib abs hitstr

L24  ANSWER 1 OF 9  USPATFULL on STN
AN     2003:226374  USPATFULL
TI     Genetic polymorphisms in the preprotachy kinin gene
IN     Foernzler, Dorothee, Lenzburg, SWITZERLAND
       Hashimoto, Lara, Basle, SWITZERLAND
       Li, Jia, Union City, CA, UNITED STATES
       Luedin, Eric, Liestal, SWITZERLAND
       Sleight, Andrew, Riedisheim, FRANCE
       Vankan, Pierre, Basle, SWITZERLAND
PI     US 2003158187      A1   20030821
AI     US 2003-354693     A1   20030130 (10)
PRAI   EP 2002-1937        20020131
DT     Utility
FS     APPLICATION
LREP   HOFFMANN-LA ROCHE INC., PATENT LAW DEPARTMENT, 340 KINGSLAND STREET,
```
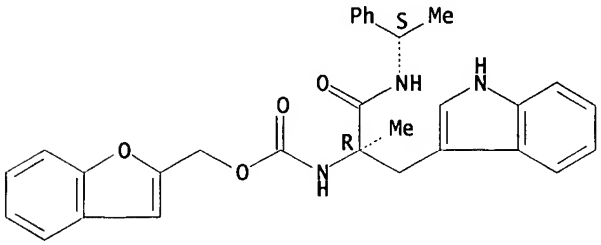

NUTLEY, NJ, 07110
CLMN Number of Claims: 31
ECL Exemplary Claim: 1
DRWN 6 Drawing Page(s)
LN.CNT 1444
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a method for correlating single nucleotide polymorphisms in the preprotachykinin (NKNA) gene with the efficacy and compatibility of a pharmaceutically active compound administered to a human being. The invention further relates to a method for determining the efficacy and compatibility of a pharmaceutically active compound administered to a human being which method comprises determining at least one single nucleotide polymorphism in the NKNA gene. Said methods are based on determining specific single nucleotide polymorphisms in the NKNA gene and determining the efficacy and compatibility of a pharmaceutically active compound in the human by reference to polymorphism in NKNA. The invention further relates to isolated nucleic acids comprising within their sequence the polymorphisms as defined herein, to nucleic acid primers and oligonucleotide probes capable of hybridizing to such nucleic acids and to a diagnostic kit comprising one or more of such primers and probes for detecting a polymorphism in the NKNA gene, to a pharmaceutical pack comprising NK-1 receptor antagonists and instructions for administration of the drug to human beings tested for the polymorphisms as well as to a computer readable medium with the stored sequence information for the polymorphisms in the NKNA gene.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **158991-23-2**, PD 154075
(NK-1 receptor antagonist; method for correlating preprotachykinin gene (NKNA) polymorphisms with efficacy and compatibility of pharmaceutically active compds., such as NK-1 receptor antagonists)
RN 158991-23-2 USPATFULL
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

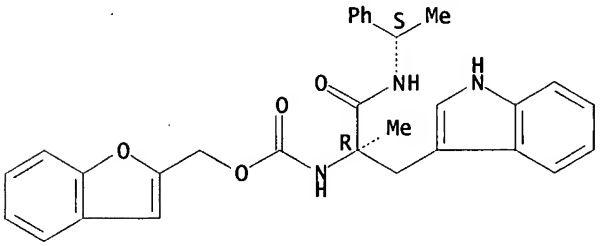


L24 ANSWER 2 OF 9 USPATFULL on STN
AN 2003:159802 USPATFULL
TI Brain, spinal, and nerve injury treament
IN Nimmo, Alan John, Townsville, AUSTRALIA
Vink, Robert, Pasadena, AUSTRALIA
PI US 2003109417 A1 20030612
AI US 2002-181323 A1 20021015 (10)
WO 2001-AU46 20010118
PRAI AU 2000-5146 20000118
DT Utility
FS APPLICATION
LREP HOFFMANN-LA ROCHE INC., PATENT LAW DEPARTMENT, 340 KINGSLAND STREET, NUTLEY, NJ, 07110
CLMN Number of Claims: 33
ECL Exemplary Claim: 1

DRWN 1 Drawing Page(s)
LN.CNT 571
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A treatment for brain, spinal and nerve injury comprising use of a substance P receptor antagonist optionally in combination with a magnesium compound. There is also provided a formulation for use in this treatment comprising a substance P receptor antagonist and a magnesium compound.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **158991-23-2**, PD-154075
(substance P receptor antagonist and optional magnesium compd. for treatment of brain, spinal and nerve injury)
RN 158991-23-2 USPATFULL
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 3 OF 9 USPATFULL on STN
AN 2003:134646 USPATFULL
TI Use of substance P antagonists for the treatment of chronic fatigue syndrome and/or fibromyalgia and use of NK-1 receptor antagonists for the treatment of chronic fatigue syndrome
IN Farber, Lothar, Heroldsberg, GERMANY, FEDERAL REPUBLIC OF
Mueller, Wolfgang, Binningen, SWITZERLAND
Stratz, Thomas, Bad Sackingen, GERMANY, FEDERAL REPUBLIC OF
PI US 2003092735 A1 20030515
AI US 2002-222060 A1 20020816 (10)
RLI Continuation of Ser. No. US 2001-792801, filed on 23 Feb 2001, PENDING
Continuation of Ser. No. WO 1999-EP6215, filed on 24 Aug 1999, UNKNOWN
PRAI GB 1998-18467 19980825
GB 1998-26692 19981204
DT Utility
FS APPLICATION
LREP THOMAS HOXIE, NOVARTIS CORPORATION, PATENT AND TRADEMARK DEPT, 564 MORRIS AVENUE, SUMMIT, NJ, 079011027
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 666
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the pharmaceutical use of specific substance P antagonists, in particular 1-acylpiperidine substance P antagonists, especially N-benzoyl-2-benzyl-4-(azanaphthoyl-amino)-piperidines, e.g. of formula ##STR1##

wherein X and Y are each independently of the other N and/or CH and the ring A is unsubstituted or mono- or poly-substituted by substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro and trifluoromethyl; and pharmnaceutically acceptable salts thereof for treatment of chronic fatigue syndrome (CFS) in the absence of serotonin agonist/selective serotonin reuptake inhibitory

therapy, or for the treatment of fibromyalgia or associated functional symptoms.

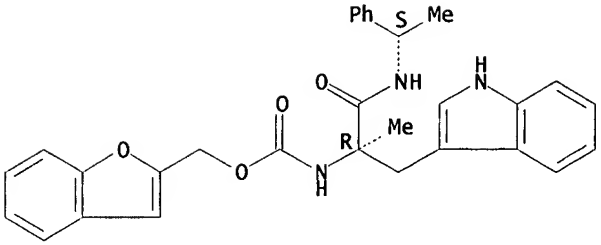
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L24 ANSWER 4 OF 9 USPATFULL on STN
AN 2003:4118 USPATFULL
TI Use of NK-1 receptor antagonists against benign prostatic hyperplasia
IN Buser, Susanne, Frenkendorf, SWITZERLAND
Ford, Anthony P.D.W., Mountain View, CA, UNITED STATES
Hoffmann, Torsten, Weil am Rhein, GERMANY, FEDERAL REPUBLIC OF
Lenz, Barbara, Bad Krozingen, GERMANY, FEDERAL REPUBLIC OF
Sleight, Andrew John, Riedisheim, FRANCE
Vankan, Pierre, Basel, SWITZERLAND
PI US 2003004157 A1 20030102
AI US 2002-71570 A1 20020208 (10)
PRAI EP 2001-109853 20010423
DT Utility
FS APPLICATION
LREP Rohan Peries, Roche Bioscience, Patent Law Dept. M/S A2-250, 3401 Hillview Avenue, Palo Alto, CA, 94304
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1676
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of an NK-1 receptor antagonist for the treatment or prevention of benign prostatic hyperplasia (BPH). The preferred NK-1 receptor antagonists are compounds of the general formula ##STR1##

wherein the meanings of R, R.sup.1, R.sup.2, R.sup.2', R.sup.3, R.sup.4 are explained in the specification and the pharmaceutically acceptable acid addition salts and the prodrugs thereof Preferred compounds are 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide, 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide, 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1.lambda..sup.6-thiomorpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide and 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1.lambda..sup.6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide. The invention also relates to pharmaceutical composition comprising one or more such NK-1 receptor antagonists and a pharmaceutically acceptable excipient for the treatment and/or prevention of benign prostatic hyperplasia.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **158991-23-2**, PD 154075
(prepn. and use of amides as NK-1 receptor antagonists against benign prostatic hyperplasia)
RN 158991-23-2 USPATFULL
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

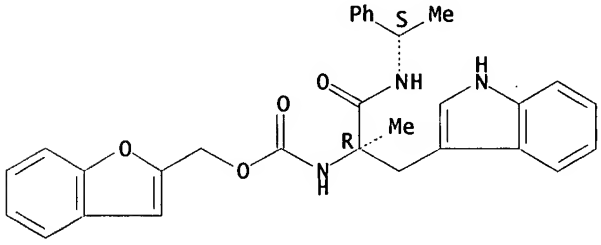
Absolute stereochemistry.



L24 ANSWER 5 OF 9 USPATFULL on STN
AN 2002:27435 USPATFULL
TI Method of treating symptoms of hormonal variation, including hot flashes, using tachykinin receptor antagonist
IN Guttuso, Thomas J., JR., Rochester, NY, UNITED STATES
PI US 2002016283 A1 20020207
AI US 2001-879390 A1 20010612 (9)
PRAI US 2000-211116P 20000612 (60)
DT Utility
FS APPLICATION
LREP Michael L. Goldman, NIXON PEABODY LLP, Clinton Square, P.O. Box 31051, Rochester, NY, 14603
CLMN Number of Claims: 31
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 590
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a methods of treating hot flashes and symptoms of hormonal variation in a patient, which methods include providing a tachykinin receptor antagonist and administering the tachykinin receptor antagonist to a patient experiencing a symptom of hormonal variation under conditions effective to treat the symptom of hormonal variation, which symptoms of hormonal variation can include hot flashes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **158991-23-2**, PD 154075
(tachykinin receptor antagonist for treating symptoms of hormonal variation, including hot flashes)
RN 158991-23-2 USPATFULL
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



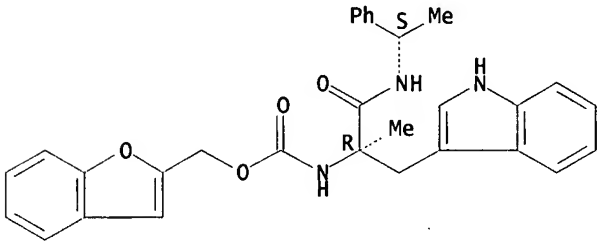
L24 ANSWER 6 OF 9 USPATFULL on STN
AN 2001:107883 USPATFULL
TI Prodrugs of benzofuranylethyl carbamate NK1 antagonists
IN Chen, Michael Huai Gu, Ann Arbor, MI, United States

Goel, Om Prakash, Ann Arbor, MI, United States
Hershenson, Fred M., Ann Arbor, MI, United States
Zhu, Zhijian, Farmington Hills, MI, United States
Chan, Oilun Helen, Canton, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 6258800 B1 20010710
WO 9952903 19991021
AI US 2000-601570 20000803 (9)
WO 1999-US6041 19990319
20000803 PCT 371 date
20000803 PCT 102(e) date
DT Utility
FS GRANTED
EXNAM Primary Examiner: Lambkin, Deborah C.; Assistant Examiner: D'Souza, Andrea
LREP Anderson, Elizabeth M., Ashbrook, Charles W.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1352
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB ##STR1##

The instant invention provides aqueous soluble prodrugs of formula (I) or a pharmaceutically acceptable salt thereof wherein R is --CH.sub.2 OZ, --C(.dbd.O)OCH.sub.2 OZ or Z, wherein Z is formula (a), --P(.dbd.O)(OH).sub.2 or --C(.dbd.O)Q: n is an integer of from 0 to 3; m is an integer of from 0 to 1, of certain tachykinin antagonists (NK.sub.1 antagonists) useful in the treatment of emesis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **158991-23-2**
(prepn. of prodrugs of benzofuranylmethyl carbamate NK1 antagonists)
RN 158991-23-2 USPATFULL
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

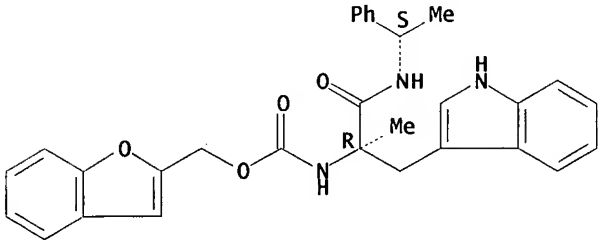


L24 ANSWER 7 OF 9 USPATFULL on STN
AN 2001:89352 USPATFULL
TI NONVOLATILE SEMICONDUCTOR MEMORY DEVICE STRUCTURE WITH SUPERIMPOSED BIT LINES AND SHORT-CIRCUIT METAL STRIPS
IN ZATELLI, NICOLA, BERGAMO, Italy
PIO, FEDERICO, BRUGHERIO, Italy
VAJANA, BRUNO, BERGAMO, Italy
PI US 2001001492 A1 20010524
US 6307229 B2 20011023
AI US 1998-81881 A1 19980519 (9)
PRAI IT 1997-MI1167 19970520
DT Utility
FS APPLICATION

LREP SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 6 Drawing Page(s)
LN.CNT 450
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A nonvolatile semiconductor memory device structure having a matrix of memory cells in a semiconductor material layer. The memory cells are located at intersections of rows and columns of the matrix. Each memory cell includes a control gate electrode connected to one of the rows, a first electrode connected to one of the columns and a second electrode. The rows comprise polysilicon strips extending parallel to each other in a first direction, and the columns are formed by metal strips extending parallel to each other in a second direction orthogonal to the first direction. Short-circuit metal strips are coupled for short-circuiting the second electrodes of the memory cells. The columns and the short-circuit strips are respectively formed in a first metal level and a second metal level superimposed on each other and electrically insulated by a dielectric layer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **158991-23-2**
(prepn. of prodrugs of benzofuranylmethyl carbamate NK1 antagonists)
RN 158991-23-2 USPATFULL
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

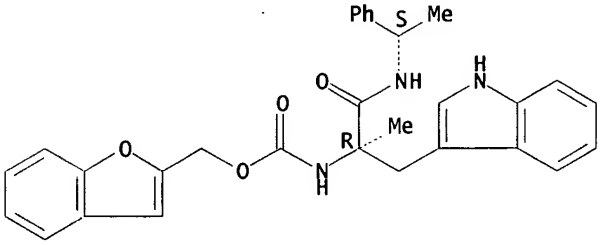


L24 ANSWER 8 OF 9 USPATFULL on STN
AN 1999:160051 USPATFULL
TI Use of a tachykinin antagonist for the manufacture of a medicament for the treatment of emesis
IN Horwell, David Christopher, Cambridge, United Kingdom
Hughes, John, Cambridge, United Kingdom
Pritchard, Martyn Clive, Cambridgeshire, United Kingdom
Singh, Lakhbir, Cambridgeshire, United Kingdom
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 5998435 19991207
WO 9749393 19971231
AI US 1998-194620 19981201 (9)
WO 1997-US10503 19970618
19981201 PCT 371 date
19981201 PCT 102(e) date
PRAI US 1996-21030P 19960626 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Menley, III, Raymond
LREP Anderson, Elizabeth M.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1

DRWN 13 Drawing Figure(s); 13 Drawing Page(s)
LN.CNT 425
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The instant invention is directed to a method for the treatment of emesis comprising administering the compound [R,S]-[2-(1H-Indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoly)-ethyl]-carbamic acid benzofuran-2ylmethyl ester.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **158991-23-2**
(tachykinin antagonist carbamate deriv. for emesis treatment)
RN 158991-23-2 USPATFULL
CN Carbamic acid, [(1R)-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[(1S)-1-phenylethyl]amino]ethyl]-, 2-benzofuranylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



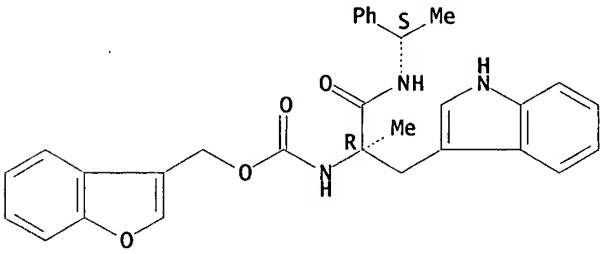
L24 ANSWER 9 OF 9 USPATFULL on STN
AN 97:3869 USPATFULL
TI Tachykinin antagonists
IN Horwell, David C., Foxton, England
Howson, William, Weston Colville, England
Pritchard, Martyn C., St. Ives, England
Roberts, Edward, Wood Ditton, England
Rees, David C., Glasgow, Scotland
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 5594022 19970114
AI US 1994-344064 19941129 (8)
RLI Continuation-in-part of Ser. No. US 1993-97264, filed on 23 Jul 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-930252, filed on 13 Aug 1992, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Springer, David B.
LREP Anderson, Elizabeth M.
CLMN Number of Claims: 51
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3534
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention concerns tachykinin antagonists. The compounds are nonpeptides which have utility in treating disorders mediated by tachykinins. Such disorders are respiratory, inflammatory, gastrointestinal, ophthalmic, allergies, pain, vascular, diseases of the central nervous system, and migraine. Methods of preparing compounds and novel intermediates are also included.

The compounds are expected to be especially useful in asthma and rheumatoid arthritis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **169475-89-2P**

(prepn. of tryptophan derivs. as tachykinin antagonists)
RN 169475-89-2 USPATFULL
CN Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 3-benzofuranylmethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



=> d his l25-

(FILE 'USPATFULL' ENTERED AT 12:07:51 ON 28 OCT 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 12:13:01 ON 28 OCT 2003

FILE 'CAPLUS' ENTERED AT 12:13:54 ON 28 OCT 2003

FILE 'USPATFULL' ENTERED AT 12:16:04 ON 28 OCT 2003

FILE 'BIOSIS' ENTERED AT 12:17:40 ON 28 OCT 2003
L25 14 S L20
L26 9 S L25 AND PY<=1999
L27 0 S L25 AND P/DT
L28 8 S L25 AND (HUGHES J? OR SINGH L?)/AU
L29 12 S L26 OR L28

=> b biosis
FILE 'BIOSIS' ENTERED AT 12:22:56 ON 28 OCT 2003
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 22 October 2003 (20031022/ED)

FILE RELOADED: 19 October 2003.

=> d all tot l29

L29 ANSWER 1 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:354835 BIOSIS
DN PREV200100354835
TI Utilization of an intramolecular hydrogen bond to increase the CNS penetration of an NK1 receptor antagonist.
AU Ashwood, Valerie A.; Field, Mark J.; Horwell, David C.; Julien-Larose, Christine; Lewthwaite, Russell A. [Reprint author]; McCleary, Scott; Pritchard, Martyn C.; Raphy, Jenny; **Singh, Lakhbir**
CS Pfizer Global Research and Development, Cambridge University, Robinson Way, Forvie Site, Cambridge, CB2 2QB, UK
Russell.Lewthwaite@Pfizer.com
SO Journal of Medicinal Chemistry, (July 5, 2001) Vol. 44, No. 14, pp. 2276-2285. print.

CODEN: JMCMAR. ISSN: 0022-2623.
DT Article
LA English
ED Entered STN: 2 Aug 2001
Last Updated on STN: 19 Feb 2002
AB This paper describes the synthesis and physical and biological effects of introducing different substituents at the alpha-position of the tryptophan containing neurokinin-1 receptor antagonist ((R)-2-(1H-indol-3-yl)-1-methyl-1-((S)-1-phenyl-ethylcarbamoyl)-ethyl)-carbamic acid benzofuran-2-ylmethyl ester (**CI 1021**). The described compounds all exhibit less than 5 nM binding affinities for the human neurokinin-1 receptor and selectivity over the tachykinin NK2 and NK3 receptor subtypes. Application of variable temperature nuclear magnetic resonance spectroscopy studies of the amide and urethane protons was utilized to determine the existence of an intramolecular hydrogen bond. This intramolecular hydrogen bond increases the apparent lipophilicity to allow increased central nervous system penetration and pharmacological activity (gerbil foot tap test) in the case of the highest affinity compound ((S)-1-dimethylaminomethyl-2-(1H-indol-3-yl)-1-((S)-1-phenyl-ethylcarbamoyl)-ethyl)-carbamic acid benzofuran-2-ylmethyl ester (PD 174424) over those analogues that could not form an intramolecular hydrogen bond.
CC Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Nervous system - Physiology and biochemistry 20504
IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
CNS: nervous system, central nervous system
IT Chemicals & Biochemicals
[(R)-2-(1H-indol-3-yl)-1-methyl-1-((S)-1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester: neurokinin-1 receptor antagonist; [(S)-1-dimethylaminomethyl-2-(1H-indol-3-yl)-1-((S)-1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester; amide protons; intramolecular hydrogen bond: utilization; neurokinin-1 receptor antagonist [NK-1 receptor antagonist]: central nervous system penetration; tryptophan: alpha-position; urethane protons
IT Methods & Equipment
NMR spectroscopy: analytical method, spectroscopic techniques: CB; gerbil foot tap test: analytical method
IT Miscellaneous Descriptors
lipophilicity
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 54-12-6Q (tryptophan)
73-22-3Q (tryptophan)

L29 ANSWER 2 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:426195 BIOSIS
DN PREV200000426195
TI Evaluation of selective NK1 receptor antagonist **CI-1021** in animal models of inflammatory and neuropathic pain.
AU Gonzalez, Maria I.; Field, Mark J.; **Hughes, John; Singh, Lakhbir** [Reprint author]
CS Parke-Davis Neuroscience Research Centre, Cambridge University Forvie Site, Robinson Way, Cambridge, CB2 2QB, UK
SO Journal of Pharmacology and Experimental Therapeutics, (August, 2000) Vol. 294, No. 2, pp. 444-450. print.
CODEN: JPETAB. ISSN: 0022-3565.

DT Article
LA English
ED Entered STN: 4 Oct 2000
Last Updated on STN: 10 Jan 2002
AB **CI-1021** (((2-benzofuran)-CH2OCO)-(R)-alpha-MeTrp-(S)-NHCH(CH3)Ph) is a selective and competitive neurokinin-1 (NK1) receptor antagonist. This study examines its activity in animal models of inflammatory and neuropathic pain. In mice, **CI-1021** (1-30 mg/kg, s.c.) dose dependently blocked the development of the late phase of the formalin response with a minimum effective dose (MED) of 3 mg/kg. Two chemically unrelated NK1 receptor antagonists, CP-99,994 (3-30 mg/kg) and SR 140333 (1-100 mg/kg), also dose dependently blocked the late phase, with respective MEDs of 3 and 10 mg/kg. PD 156982, a NK1 receptor antagonist with poor central nervous system penetration, failed to have any effect. However, when administered i.c.v., it selectively blocked the late phase of the formalin response. Chronic constrictive injury (CCI) to a sciatic nerve in the rat induced spontaneous pain, thermal and mechanical hyperalgesia, and cold, dynamic, and static allodynia. **CI-1021** (10-100 mg/kg) and morphine (3 mg/kg) blocked all the responses except dynamic allodynia. Carbamazepine (100 mg/kg) was weakly effective against all the responses. Once daily administration of morphine (3 mg/kg, s.c.) in CCI rats led to the development of tolerance within 6 days. Similar administration of **CI-1021** (100 mg/kg, s.c.) for up to 10 days did not induce tolerance. Moreover, the morphine tolerance failed to cross-generalize to **CI-1021** . **CI-1021** blocked the CCI-induced hypersensitivity in the guinea pig, with a MED of 0.1 mg/kg, p.o. **CI-1021** (10-100 mg/kg, s.c.) did not show sedative/ataxic action in the rat rota-rod test. It is suggested that NK1 receptor antagonists possess a superior side effect profile to carbamazepine and morphine and may have a therapeutic use for the treatment of inflammatory and neuropathic pain.
CC Pharmacology - General 22002
Biochemistry studies - General 10060
Pathology - Therapy 12512
Nervous system - Physiology and biochemistry 20504
IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination); Pharmacology
IT Parts, Structures, & Systems of Organisms
sciatic nerve: nervous system, chronic constrictive injury
IT Chemicals & Biochemicals
CP-99,994: neurokinin-1 receptor antagonist; Cl-1021: NK-1 receptor antagonist, evaluation, neurokinin-1 receptor antagonist; PD 156982: neurokinin-1 receptor antagonist; SR 140333: neurokinin-1 receptor antagonist; carbamazepine; morphine; neurokinin-1
IT Miscellaneous Descriptors
pain: inflammatory, neuropathic
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Sprague-Dawley rat: animal model, male
mouse: animal model, male, strain-BKTO
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 136982-36-0 (CP-99,994)
210481-96-2 (PD 156982)
155418-05-6 (SR 140333)
298-46-4 (carbamazepine)
57-27-2 (morphine)

L29 ANSWER 3 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:330071 BIOSIS
DN PREV200000330071
TI Gabapentin and the NK1 receptor antagonist CI-1021 act

synergistically to block allodynia induced in a rat model of neuropathic pain.
AU Field, M. J. [Reprint author]; McCleary, S. [Reprint author]; Singh, L. [Reprint author]
CS Parke-Davis Neuroscience Research Centre, Robinson Way, Forvie Site, Cambridge, CB2 2QB, UK
SO British Journal of Pharmacology, (January, 2000) Vol. 129, No. Proceedings Supplement, pp. 79P. print.
Meeting Info.: Meeting of the British Pharmacological Society. Cambridge, England, UK. January 05-07, 2000. British Pharmacological Society.
CODEN: BJPCBM. ISSN: 0007-1188.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 2 Aug 2000
Last Updated on STN: 7 Jan 2002
CC Nervous system - General and methods 20501
Biochemistry studies - General 10060
Biophysics - General 10502
Endocrine - General 17002
General biology - Symposia, transactions and proceedings 00520
IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination)
IT Chemicals & Biochemicals
CI-1021: neurokinin type 1 receptor antagonist; gabapentin
IT Miscellaneous Descriptors
allodynia; neuropathic pain; Meeting Abstract
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Sprague-Dawley rat: animal model, male
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN **158991-23-2 (CI-1021)**
60142-96-3 (gabapentin)

L29 ANSWER 4 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:396361 BIOSIS
DN PREV199800396361
TI A Trp in chi space.
AU Horwell, D. C.; McKiernan, M. J. [Reprint author]; Naylor, D.; Osborne, S. A.
CS Parke-Davis Neurosci. Res. Cent., Cambridge Univ., Forvie Site, Robinson Way, Cambridge CB2 2QB, UK
SO Letters in Peptide Science, (May, 1998) Vol. 5, No. 2-3, pp. 143-145. print.
ISSN: 0929-5666.
DT Article
LA English
ED Entered STN: 10 Sep 1998
Last Updated on STN: 21 Oct 1998
AB Our aim is to identify and synthesize a 'family, of tryptophan mimetics which thoroughly explore chi space and then incorporate them into selected ligands for biological receptors e.g. Tachykinin NK1. This project is considered important as only the psi-variant phi angles have previously been explored; obtaining a greater understanding of the spacial orientation of the side chain in chi space (chi1 chi2) should prove invaluable to the future design of peptidomimetics. The amino acid tryptophan was selected as it has proved pivotal in many pharmaceutic drug programmes.
CC Pharmacology - General 22002
Biochemistry methods - General 10050

Biochemistry studies - General 10060
IT Major Concepts
Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
beta-disubstituted tryptophan mimetics; biological receptors; tachykinin NK-1 receptor; tryptophan; CI-988: CCKB antagonist; **PD 154 075**: tachykinin NK-1 antagonist; PD 169 099: NMB antagonist; 2,3-cyclized tryptophan mimetics; 3,4-cyclized tryptophan mimetics
IT Methods & Equipment
synthesis: Synthesis/Modification Techniques, synthetic method
IT Miscellaneous Descriptors
chi space; energy conformations; peptidomimetic design; pharmaceutic drug programs; spacial orientation
RN 54-12-6Q (tryptophan)
73-22-3Q (tryptophan)
130404-91-0 (CI-988)
158991-23-2 (PD 154 075)

L29 ANSWER 5 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:323837 BIOSIS
DN PREV199800323837
TI Involvement of the central tachykinin NK1 receptor during maintenance of mechanical hypersensitivity induced by diabetes in the rat.
AU Field, Mark J.; McCleary, Scott; Boden, Philip; Suman-Chauhan, Nirmala; **Hughes, John; Singh, Lakhbir** [Reprint author]
CS Dep. Biol., Parke-Davis, Neurosci. Res. Centre, Cambridge Univ. Forvie Site, Robinson Way, Cambridge CB2 2QB, UK
SO Journal of Pharmacology and Experimental Therapeutics, (June, 1998) Vol. 285, No. 3, pp. 1226-1232. print.
CODEN: JPETAB. ISSN: 0022-3565.
DT Article
LA English
ED Entered STN: 22 Jul 1998
Last Updated on STN: 22 Jul 1998
AB Our study examines the role of central and peripheral neurokinin, (NK1) receptors in diabetes-induced mechanical hypersensitivity. Glycine, N, N-dimethyl-, 2-((2-(((2-benzofuranylmethoxy)carbonyl)amino)-3-(1H-indol-3-y;)-2-methyl-1-oxopropyl) amino)-2-phenylethylester, bisulfate, (R-(R*,R)) (PD 156982) is a selective NK1 receptor antagonist with nanomolar affinity for the human (IC50 = 1.4 nM) and guinea pig (IC50 = 9.6 nM) NK1 receptors. However, it has approximately two orders of magnitude lower affinity for the rodent NK, receptor (IC50 = 820 nM). In electrophysiological studies, PD 156982 inhibited NK, receptor-mediated responses in the guinea pig locus ceruleus, in a competitive manner, with an equilibrium constant of 13.9 nM. The intracerebroventricular (10-100 mug/animal) but not systemic administration of PD 156982 (1-100 mg/kg, s.c.) blocked the (Sar9Met(O2)11) substance P-induced gerbil foot tapping response. This indicates that PD 156982 is unable to penetrate into the central nervous system. However, PD 156982 (10-100 mg/kg, s.c.) blocked the mechanical hypersensitivity induced by administration of substance P into the plantar surface of a rat paw. This suggests that PD 156982 can effectively antagonize peripheral NK1 receptors in vivo. The chemically related compound carbamic acid, (1-(1H-indol-3-yl-methyl)-1-methyl-2-oxo-2-((1-phenylethyl)amino)ethyl)-, 2-benzofuranylmethyl ester, (R-(R*,S*)) (Cl-1021) is also a selective NK, receptor antagonist but can penetrate into the central nervous system. PD 156982 (10-100 mg/kg, s.c.) failed to block streptozocin (75 mg/kg, i.p.) induced mechanical hypersensitivity. In contrast, Cl-1021 dose-dependently (3-100 mg/kg, s.c.) blocked this hypersensitivity state with a minimum effective dose of 10 mg/kg. At these doses CI-1 021 also antagonized mechanical hypersensitivity mediated by central NK1 but not NK2 receptors in the rat. It is suggested that the central NK1 receptor may play an important role in diabetes-induced hypersensitivity.
CC Pharmacology - General 22002
Behavioral biology - Animal behavior 07003
Biochemistry studies - General 10060

Biophysics - General 10502
Metabolism - Metabolic disorders 13020
Endocrine - General 17002
Nervous system - General and methods 20501
IT Major Concepts
Biochemistry and Molecular Biophysics; Metabolism; Nervous System (Neural Coordination); Pharmacology
IT Diseases
diabetes: endocrine disease/pancreas, metabolic disease
Diabetes Mellitus (MeSH)
IT Chemicals & Biochemicals
glycine; neurokinin receptors: central, peripheral; substance P; **CI-1021**: neurokinin receptor antagonist; PD 156982: neurokinin receptor antagonist
IT Miscellaneous Descriptors
mechanical hypersensitivity
ORGN Classifier
Caviidae 86300
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
guinea-pig
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Cricetidae 86310
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Mongolian gerbil: female, male
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Sprague-Dawley rat: male
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 56-40-6 (glycine)
33507-63-0 (substance P)
158991-23-2 (CI-1021)
210481-96-2 (PD 156982)

L29 ANSWER 6 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:286356 BIOSIS
DN PREV199800286356
TI Anti-emetic effects of **PD154075** (CAM-4261) in different emetic models in the ferret.
AU Chevalier, E. [Reprint author]; **Singh**, L.; Diop, L. [Reprint author]
CS Jouveinal, Park-Davis, Fresnes, France
SO Gastroenterology, (April 15, 1998) Vol. 114, No. 4 PART 2, pp. A578. print.
Meeting Info.: Digestive Disease Week and the 99th Annual Meeting of the

American Gastroenterological Association. New Orleans, Louisiana, USA. May 16-22, 1998. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 8 Jul 1998
Last Updated on STN: 13 Aug 1998
CC Pharmacology - General 22002
Digestive system - General and methods 14001
General biology - Symposia, transactions and proceedings 00520
IT Major Concepts
Dental and Oral System (Ingestion and Assimilation); Pharmacology
IT Chemicals & Biochemicals
PD154075 [CAM-4261]: antiemetic-drug
IT Miscellaneous Descriptors
emetic models; Meeting Abstract
ORGN Classifier
Mustelidae 85780
Super Taxa
Carnivora; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
ferret
Taxa Notes
Animals, Carnivores, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
RN **158991-23-2 (PD154075)**
158991-23-2 (CAM-4261)

L29 ANSWER 7 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:233202 BIOSIS
DN PREV199800233202
TI Evaluation of **PD 154075**, a tachykinin NK1 receptor antagonist, in a rat model of postoperative pain.
AU Gonzalez, M. Isabel; Field, Mark J.; Holloman, Elizabeth F.; **Hughes, John**; Oles, Ryszard J.; **Singh, Lakhbir** [Reprint author]
CS Dep. Biol., Parke-Davis Neuro. Res. Cent., Cambridge Univ. Forvie Site, Robinson Way, Cambridge CB2 2QB, UK
SO European Journal of Pharmacology, (March 5, 1998) Vol. 344, No. 2-3, pp. 115-120. print.
CODEN: EJPHAZ. ISSN: 0014-2999.
DT Article
LA English
ED Entered STN: 20 May 1998
Last Updated on STN: 20 May 1998
AB **PD 154075** (((2-benzofuran)-CH2OCO)-(R)-alpha-MeTrp-(S)-NHCH(CH3)Ph) is a selective tachykinin NK, receptor antagonist. Its effect on development and maintenance of thermal and mechanical hypersensitivity was examined in a rat model of surgical pain. When administered 30 min before surgery, **PD 154075** dose-dependently (3-100 mg/kg, s.c.) prevented the development of thermal and mechanical hypersensitivity with respective minimum effective doses of 10 and 30 mg/kg. These antihypersensitivity effects lasted for 72 h. In contrast, the administration of **PD 154075** (30 mg/kg, s.c.) after surgery had little or no effect on these nociceptive responses. **PD 154075** antagonised thermal hypersensitivity induced by intrathecal administration of substance P, over the same dose range that blocked surgical hypersensitivity. However, it only partially blocked the thermal hypersensitivity induced by the selective NK2 receptor agonist (betaAla8)neurokinin A-(4-10). Morphine dose-dependently (1-6 ma/kg, s.c.) lengthened isoflurane and pentobarbitone-induced sleeping time in the rat. In contrast, **PD 154075** (3-100 mg/kg, s.c.) did not interact with these anaesthetics. It is suggested that tachykinin NK1 receptor antagonists, such as **PD 154075**, may possess therapeutic potential as pre-emptive antihypersensitive agents.
CC Pharmacology - Neuropharmacology 22024

Cytology - Animal 02506
Pathology - Therapy 12512
Endocrine - General 17002
Nervous system - Anatomy 20502
Nervous system - Physiology and biochemistry 20504
Pharmacology - Drug metabolism and metabolic stimulators 22003
Biochemistry studies - General 10060
Biochemistry studies - Lipids 10066
IT Major Concepts
Nervous System (Neural Coordination); Pharmacology
IT Diseases
postoperative pain: nervous system disease, rat model
Pain, Postoperative (MeSH)
IT Chemicals & Biochemicals
PD 154075: analgesic-drug, tachykinin NK-1 receptor antagonist, pharmacodynamics
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN **158991-23-2 (PD 154075)**

L29 ANSWER 8 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:52381 BIOSIS
DN PREV199800052381
TI Tetrahydro-pyrrolo-(2,3-b)indole-1,2,8-tricarboxylic acid ester in enantiospecific preparation of alpha-methyltryptophan: Application in the preparation of carbon-14 labeled PD 145942 and **PD 154075**
.
AU Ekhato, I. Victor; Huang, Yun
CS Dep. Chem. Development, Parke-Davis Pharm. Res. Div., Warner-Lambert Co., Ann Arbor, MI 48105, USA
SO Journal of Labelled Compounds and Radiopharmaceuticals, (Dec., 1997) Vol. 39, No. 12, pp. 1019-1038. print.
CODEN: JLCRD4. ISSN: 0362-4803.
DT Article
LA English
ED Entered STN: 27 Jan 1998
Last Updated on STN: 20 Mar 1998
AB (2R-(2alpha, 3alphabeta, 8alphabeta))-2,3,3a,8a-Tetrahydra-pyrrolo(2,3-b)indole-1,2,8-tricarboxylic acid-1,8-dibenzyl ester 2-methyl ester, its (2S-(2beta, 3aalpha, 8aalpha))-isomer, and the tribenzyl ester analogs were prepared. From these (2,3-b)indole-1,2,8-tricarboxylic acid esters we accomplished a simple, high yielding preparation of enantiopure alpha-methyltryptophan and methyl ester derivatives. Using this protocol, we inexpensively made (R)-alpha-(14C)methyltryptophan methyl ester, and in subsequent reactions converted it into (1-(2-hydroxy-cyclohexylcarbamoyl)-2-(1H-indol-3-yl)-1-(14C)methyl-ethyl)carbamic acid adamantan-2-yl ester (PD 145942) and (2-(1H-indole-3-yl)-1-(14C)methyl-1(1-phenyl-ethylcarbamoyl)-ethyl)carbamic acid benzofuran-2-yl methyl ester (**PD 154075**). Both of these compounds are drug candidates in preclinical study for the treatment of anxiety and emesis respectively.
CC Pharmacology - General 22002
Biochemistry methods - General 10050
Biochemistry studies - General 10060
IT Major Concepts
Pharmacology
IT Diseases
anxiety: behavioral and mental disorders
Anxiety (MeSH)
IT Diseases
emesis: digestive system disease

IT Chemicals & Biochemicals
alpha-methyltryptophan: enantiospecific preparation; methylester derivatives; tetrahydro-pyrrolo-[2,3-b]indole-1,2,8-tricarboxylic acid ester; PD 145942: carbon-14 labelled; **PD 154075**: carbon-14 labelled
IT Miscellaneous Descriptors
drug candidates
RN 153-91-3 (alpha-methyltryptophan)
158991-23-2 (PD 154075)

L29 ANSWER 9 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:470480 BIOSIS
DN PREV199799769683
TI Effects of the selective NK-1 receptor antagonist **PD 154075** on plasma protein extravasation in guinea-pig airways.
AU Meecham, K. [Reprint author]; Purbrick, S. [Reprint author]; Blyth, K. [Reprint author]; Planquois, J.-M.; Mottin, G.; Payne, A.; **Hughes**, J. [Reprint author]; Williams, R. [Reprint author]
CS Parke-Davis Neurosci. Res. Centre, Forvie Site, Robinson Way, Cambridge CB2 2QB, UK
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 674. Meeting Info.: 27th Annual Meeting of the Society for Neuroscience, Part 1. New Orleans, Louisiana, USA. October 25-30, 1997. ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 4 Nov 1997
Last Updated on STN: 10 Dec 1997
CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Membrane phenomena 10508
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Neuropharmacology 22024
IT Major Concepts
Membranes (Cell Biology); Pharmacology
IT Chemicals & Biochemicals
PD 154075
IT Miscellaneous Descriptors
EXTRAVASATION; NERVOUS SYSTEM; NK1 RECEPTOR ANTAGONIST; **PD 154075**; PHARMACODYNAMICS; PHARMACOLOGY; PLASMA PROTEIN
ORGN Classifier
Caviidae 86300
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
guinea-pig
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN **158991-23-2 (PD 154075)**

L29 ANSWER 10 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:173442 BIOSIS
DN PREV199799480045
TI The tachykinin NK-1 receptor antagonist **PD 154075** blocks cisplatin-induced delayed emesis in the ferret.
AU **Singh, Lakhbir** [Reprint author]; Field, Mark J.; **Hughes, John**; Kuo, Be-Sheng; Suman-Chauhan, Nirmala; Tuladhar, Bishwa R.; Wright, D. Scott; Naylor, Robert J.
CS Dep. Biol., Parke-Davis Neurosci. Res. Centre, Cambridge Univ. Forvie Site, Robinson Way, Cambridge CB2 2QB, UK
SO European Journal of Pharmacology, (1997) Vol. 321, No. 2, pp. 209-216. CODEN: EJPHAZ. ISSN: 0014-2999.
DT Article
LA English

ED Entered STN: 24 Apr 1997
Last Updated on STN: 2 Jun 1997

AB The activity of a selective tachykinin NK-1 receptor antagonist, **PD 154075** (((2-benzofuran)-CH-2OCO)-(R)-alpha-MeTrp-(S)-NHCH(CH-3)Ph), was examined in radioligand binding studies, in a (Sar-9,Met(O-2)-11)substance P-induced foot-tapping model in the gerbil, and in cisplatin-induced acute and delayed emesis in the ferret. In radioligand binding studies, **PD 154075** showed nanomolar affinity for the human, guinea-pig, gerbil, dog and ferret NK-1 receptors with an approximate 300 times lower affinity for the rodent NK-1 receptor. Using NK-2, NK-3 receptors and a range of other receptor ligands, **PD 154075** was shown to exhibit a high degree of selectivity and specificity for the human type NK, receptor. Following subcutaneous administration **PD 154075** dose dependently (1-100 mg/kg) antagonised the centrally mediated (Sar-9,Met(O-2)-11) substance P-induced foot tapping in the gerbil with a minimum effective dose (MED) of 10 mg/kg. The ability of **PD 154075** to readily penetrate into the brain following oral administration was confirmed by its extraction and high performance liquid chromatography assay from the rat brain. **PD 154075** was shown to achieve a relatively fast and sustained brain concentration (brain/plasma ratios ranged from 0.27 to 0.41 during the time period of 0.25-12 h). Further pharmacokinetic studies revealed that the absolute oral bioavailability of **PD 154075** in the rat was (mean +- S.D.) 49 +- 15%. **PD 154075** (1-30 mg/kg, i.p.) dose dependently antagonised the acute vomiting and retching in the ferret measured for 4 h following administration of cisplatin (10 mg/kg, i.p.) with a MED of 3 mg/kg. The administration of a lower dose of cisplatin (5 mg/kg, i.p.) in the ferret induces both an acute (day 1) and delayed (days 2 and 3) phase of emesis. The i.p. administration of **PD 154075**, 10 mg/kg three times a day for 3 days, almost completely blocked both the acute and delayed emetic responses. In the same study, the 5-HT-3 receptor antagonist ondansetron (1 mg/kg, i.p., t.i.d.) was also very effective against the acute emetic response observed during the first 4 h following cisplatin, but it was only weakly active against the delayed response. In conclusion, **PD 154075** is a selective and specific high affinity NK-1 receptor antagonist with good oral bioavailability which is effective against both acute and delayed emesis induced by cisplatin in the ferret.

CC Cytology - Animal 02506
Cytology - Human 02508
Comparative biochemistry 10010
Biochemistry studies - General 10060
Biochemistry studies - Minerals 10069
Biophysics - Membrane phenomena 10508
Digestive system - Pathology 14006
Endocrine - Neuroendocrinology 17020
Nervous system - Physiology and biochemistry 20504
Toxicology - Pharmacology 22504
Toxicology - Antidotes and prevention 22505
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Gastroenterology (Human Medicine, Medical Sciences); Membranes (Cell Biology); Nervous System (Neural Coordination); Oncology (Human Medicine, Medical Sciences); Toxicology

IT Chemicals & Biochemicals
PD 154075; CISPLATIN; SUBSTANCE P

IT Miscellaneous Descriptors
ANTIDOTE-DRUG; ANTIEMETIC-DRUG; ANTINEOPLASTIC-DRUG; BIOAVAILABILITY; CISPLATIN; DIGESTIVE SYSTEM; DRUG-INDUCED DELAYED EMESIS; **PD 154075**; PHARMACODYNAMICS; PHARMACOKINETICS; PHARMACOLOGY; SUBSTANCE P; TACHYKININ NK-1 RECEPTOR ANTAGONIST; TOXICOLOGY

ORGN Classifier
Canidae 85765
Super Taxa

Carnivora; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
dog
Taxa Notes
Animals, Carnivores, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
ORGN Classifier
Caviidae 86300
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
guinea-pig
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Cricetidae 86310
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
gerbil
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Mustelidae 85780
Super Taxa
Carnivora; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
ferret
Taxa Notes
Animals, Carnivores, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
RN **158991-23-2 (PD 154075)**
15663-27-1 (CISPLATIN)
33507-63-0 (SUBSTANCE P)

L29 ANSWER 11 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:8033 BIOSIS
DN PREV199799307236
TI Brain penetration of the new lead compound **PD 154075** in rats.
AU Van Noord, Ted; Wright, D. Scott; Kuo, Be-Sheng
CS Dep. Pharmacokinetics Drug Metabolism, Parke-Davis Pharmaceutical Research, Div. Warner-Lambert Co., Ann Arbor, MI 48105, USA
SO Pharmaceutical Research (New York), (1996) Vol. 13, No. 9 SUPPL., pp. S419.
Meeting Info.: Annual Meeting of the American Association of Pharmaceutical Scientists. Seattle, Washington, USA. October 27-31, 1996.
CODEN: PHREEB. ISSN: 0724-8741.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 7 Jan 1997
Last Updated on STN: 11 Feb 1997
CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Biophysics - Molecular properties and macromolecules 10506
Biophysics - Membrane phenomena 10508

Cardiovascular system - Physiology and biochemistry 14504
Nervous system - Physiology and biochemistry 20504
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Digestive system 22014
Pharmacology - Neuropharmacology 22024
Routes of immunization, infection and therapy 22100

IT Major Concepts
Cardiovascular System (Transport and Circulation); Membranes (Cell Biology); Nervous System (Neural Coordination); Pharmacology

IT Chemicals & Biochemicals
LEAD; **PD 154075**; CP99994

IT Miscellaneous Descriptors
pharmaceutical industry; ANALYTICAL METHOD; ANTIEMETIC; BIOBUSINESS; BLOOD CONCENTRATION; BRAIN; CP99994; HIGH PERFORMANCE LIQUID CHROMATOGRAPHY; HPLC; INTRAVENOUS ADMINISTRATION; NERVOUS SYSTEM; ORAL ADMINISTRATION; **PD154075**; PD158196; PENETRATION; PHARMACEUTICALS; PHARMACOLOGY; PLASMA CONCENTRATION; SUSTAINED RELEASE

ORGN Classifier
Mammalia 85700
Super Taxa
Vertebrata; Chordata; Animalia
Organism Name
mammal
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 7439-92-1D (LEAD)
158991-23-2 (PD 154075)
136982-36-0 (CP99994)

L29 ANSWER 12 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:426649 BIOSIS
DN PREV199699157705
TI 'Targeted' molecular diversity: Design and development of non-peptide antagonists for cholecystokinin and tachykinin receptors.
AU Horwell, David [Reprint author]; Pritchard, Martyn; Raphy, Jennifer; Ratcliffe, Giles
CS Parke-Davis Neurosci. Res. Cent., Forvie Site, Robinsin Way, Cambridge CB2 2QB, UK
SO Immunopharmacology, (1996) Vol. 33, No. 1-3, pp. 68-72.
CODEN: IMMUDP. ISSN: 0162-3109.
DT Article
LA English
ED Entered STN: 26 Sep 1996
Last Updated on STN: 26 Sep 1996
AB A drug design strategy to non-peptide small molecule antagonists of neuropeptides is described that targets the molecular diversity which exists in the 'privileged' data set of the physico-chemical properties represented by the side-chains of the 20 genetically encoded amino acids. The strategy is exemplified by the design of a selective and high affinity cholecystokinin CCK-A antagonist PD 140548, CCK-B antagonist CI-988 (formerly PD 134308) tachykinin NK-1 antagonist **PD 154075** and NK-2 antagonist Cam-2291. The NK-3 antagonists, PD 157672 and the non-peptide PD 161182, were developed from an information-rich dipeptide library constructed from 256 N-protected dipeptides and 64 hydrophobic biased dipeptides.
CC Cytology - Animal 02506
Cytology - Human 02508

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     Genetics - Animal   03506
     Comparative biochemistry   10010
     Biochemistry methods - Proteins, peptides and amino acids   10054
     Biochemistry studies - Proteins, peptides and amino acids   10064
     Replication, transcription, translation   10300
     Biophysics - Molecular properties and macromolecules   10506
     Biophysics - Membrane phenomena   10508
     Reproductive system - General and methods   16501
     Endocrine - Neuroendocrinology   17020
     Nervous system - Physiology and biochemistry   20504
     Pharmacology - Drug metabolism and metabolic stimulators   22003
     Pharmacology - Immunological processes and allergy   22018
     Tissue culture, apparatus, methods and media   32500
     In vitro cellular and subcellular studies   32600
     Immunology - General and methods   34502
     Immunology - Immunopathology, tissue immunology   34508
IT   Major Concepts
        Biochemistry and Molecular Biophysics; Cell Biology; Clinical
        Endocrinology (Human Medicine, Medical Sciences); Endocrine System
        (Chemical Coordination and Homeostasis); Membranes (Cell Biology);
        Nervous System (Neural Coordination); Pharmacology
IT   Miscellaneous Descriptors
        CHINESE HAMSTER OVARY CHO CELLS; DRUG DESIGN; GENE EXPRESSION;
        IMMUNOPHARMACOLOGY; NEUROPEPTIDES; SYNTHESIS
ORGN Classifier
        Cricetidae   86310
     Super Taxa
        Rodentia; Mammalia; Vertebrata; Chordata; Animalia
     Organism Name
        Cricetidae
     Taxa Notes
        Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
        Rodents, Vertebrates
ORGN Classifier
        Hominidae   86215
     Super Taxa
        Primates; Mammalia; Vertebrata; Chordata; Animalia
     Organism Name
        human
     Taxa Notes
        Animals, Chordates, Humans, Mammals, Primates, Vertebrates


=> d his

     (FILE 'HOME' ENTERED AT 11:35:18 ON 28 OCT 2003)

     FILE 'CAPLUS' ENTERED AT 11:35:27 ON 28 OCT 2003
                E HUGHES J/AU
L1         1027 S E3-49
                E HUGHES JOHN/AU
L2          576 S E3-57
L3         1602 S L1-2
                E SINGH L/AU
L4          395 S E3-25
                E E
                E SINGH L/AU
L5           56 S E36
L6            8 S E39
L7          459 S L4-6
                E WO2000-EP10084/AP,PRN
L8            1 S E3-4
                SEL RN

     FILE 'REGISTRY' ENTERED AT 11:45:11 ON 28 OCT 2003
L9            4 S E1-4
L10           1 S L9 AND C30H29N3O4
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              E C30H29N3O4/MF
L11         213 S E3
L12         103 S L11 AND 5/NR
L13        2221 S (OC4-C6 AND NC4-C6 AND C6)/ES
L14           5 S L13 AND L12
L15           3 S L14 NOT (14C OR TRITIUM)
L16           3 S L10 OR L15
                SEL RN
L17           0 S E1-E3/CRN

     FILE 'CAPLUS' ENTERED AT 12:02:12 ON 28 OCT 2003
L18          18 S L16
L19          14 S CI 1021 OR CI1021 OR PD154075 OR PD()(154075 OR 154 075)
L20          20 S L18 OR L19
L21          10 S L20 AND (PY<=1999 OR PRY<=1999 OR AY<=1999)
L22           6 S L1-L7 AND L20
L23          12 S L21-22

     FILE 'USPATFULL' ENTERED AT 12:07:51 ON 28 OCT 2003
L24           9 S L20
                SET COST OFF

     FILE 'REGISTRY' ENTERED AT 12:13:01 ON 28 OCT 2003

     FILE 'CAPLUS' ENTERED AT 12:13:54 ON 28 OCT 2003

     FILE 'USPATFULL' ENTERED AT 12:16:04 ON 28 OCT 2003

     FILE 'BIOSIS' ENTERED AT 12:17:40 ON 28 OCT 2003
L25          14 S L20
L26           9 S L25 AND PY<=1999
L27           0 S L25 AND P/DT
L28           8 S L25 AND (HUGHES J? OR SINGH L?)/AU
L29          12 S L26 OR L28

     FILE 'BIOSIS' ENTERED AT 12:22:56 ON 28 OCT 2003
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